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CONTENTS: ORIGINAL ARTICLES

NUMBER 1, JANUARY, 1929

A Note on Laennec's Invention of the Stethoscope. WARFIELD T. LONGCOPE 1
A Study of Bacillus Calmette-Guérin (BCG). I. Biological Characteristics, Cultural "Dissociation" and Animal Experimentation. S. A. PETROFF, ARNOLD BRANCH AND WILLIAM STEENKEN, JR... 9
The Isolation of the Tubercle Bacillus from Sputum. A Comparative Study of Petroff's and of Corper and Uyei's Methods. MOTI MALKANI 47
The Testicular Allergic Response (Spermatocyte Reaction) in Guinea Pigs for the Diagnosis of Tuberculous Fluids. J. J. WIENER, JOHN E. BLAIR AND HENRY L. JAFFE 55
The Compression Therapy of Pulmonary Tuberculosis. A Comparative Study. LEROY S. PETERS 74
Blood Transfusion in Pulmonary Tuberculosis. Case Reports. W. G. GAMBLE, JR 84
Remarks on Tuberculous Pleurisy, Especially Its Treatment. E. S. BULLOCK 90
The Association of Tuberculous Lymphadenitis and Genitourinary Tuberculosis. F. J. LUSSMANN 95
A Study of 1000 Cases of Adult Tuberculosis and Its Bearing on Diagnosis. I. C. MOLONY 99

NUMBER 2, FEBRUARY, 1929

A Study of the Tuberculous Lesions in the Lung of a Negro Child Nine Weeks Old. II. A Tuberculous Lymph Node Situated in the Incisura Interlobaris with Its Afferent and Efferent Lymphatics. WILLIAM SNOW MILLER 119
Tuberculosis of the Common Crow. A Preliminary Study. CHARLES A. MITCHELL AND R. C. DUTHIE 134
Pregnancy and Pulmonary Tuberculosis. ARTHUR H. MORSE 140
Acute Subapical Versus Insidious Apical Tuberculosis. A Preliminary Report. BRUCE H. DOUGLAS, MAX PINNER AND BEN WOLEPOR.. 153
Recurring Nontuberculous Pneumonia Resulting from Cystic Overflow. EVERETT MORRIS AND CHARLES P. HARROD 174

Multiple Pulmonary Abscesses Resulting from Blood Infection by Microörganisms of the Proteus Group. M. J. KING AND R. H. MORGAN..... 182
Bronchiectasis. HAROLD BRUNN AND WILLIAM B. FAULKNER, JR... 191
Tuberculous Ulceration of the Bronchus in a Case of Lung Abscess Following Tonsillectomy. M. C. MYERSON..... 201
Diaphragmatic Studies in Tuberculosis. PAUL D. CRIMM..... 206
The Complement-Fixation Test in Different Clinical Manifestations of Tuberculosis. TH. THJÖTTA AND EDV. GUNDERSEN..... 212
Observations on the Occurrence of Nonspecific Agglutinins in Tuberculosis. ROBERT A. KILDUFFE AND WILLIAM W. HERSOHN..... 223
Pearl Mitchell Hall, 1860–1928..... 230

NUMBER 3, MARCH, 1929

The Cauterization of Adhesions in Artificial Pneumothorax by the Jacobaeus-Unverricht Method of Closed Pneumolysis. Observations on 100 Cases. RALPH C. MATSON..... 233
A Simplified Operating Thoracoscope. LOUIS R. DAVIDSON..... 306
Haemoptysis in Tuberculosis Followed by Massive Pulmonary Atelectasis. A Case Report. JULIUS L. WILSON..... 310
The Mind and Tuberculosis. BEN WOLEPOR..... 314
A Clinical Study of Tuberculin Fractions Prepared from Nonprotein Culture Media. FREDERICK EBERSON AND ERNEST WOLFF..... 327
Blood-Serum Calcium in the Negro. A Laboratory Study. C. LYDON HARRELL..... 350

NUMBER 4, APRIL, 1929

Studies on Pulmonary Acoustics. I. An Apparatus for Recording Respiratory Sounds. P. F. METILDI AND R. S. LYMAN..... 353
Studies on Pulmonary Acoustics. II. The Transmission of Tracheal Sounds through Freshly Exenterated Sheep's Lungs. R. R. HANNON AND R. S. LYMAN..... 360
Some Sources of Acid-Fast Bacilli. STEPHEN J. MAHER..... 376
Cancer of the Lungs. FREDERICK L. HOFFMAN..... 392
Tuberculosis among the American Indians..... 407
An Analysis of 1,000 Deaths from Pulmonary Tuberculosis among Insured Policy-Holders. L. H. LEE..... 412
The Experience of Philadelphia's Tuberculosis Patients in Clinics and State Sanatoria. DOROTHY E. WIESNER AND LUELLA H. SMITH. 414
Accidental Pneumoperitoneum as a Complication of Artificial Pneumothorax. LEROY ELRICK..... 427

The Use of Iodized Oil in Pulmonary Tuberculosis. EVERETT K. GEER, F. F. CALLAHAN AND D. GRETH GARDINER..... 434
Periodic Febrile Exacerbations in Pulmonary Tuberculosis. I. RAPPAPORT AND R. T. ELLISON..... 440
Cases of Erythema Nodosum with Negative Tuberculin Tests. ELSA LAGERGREN..... 447
The Sickle-Cell Phenomenon in Tuberculosis Patients. VERA B. DOLGOPOL AND RICHARD H. STITT..... 454

NUMBER 5, MAY, 1929

The Trend of Tuberculosis Mortality in Rural and Urban Areas. EDGAR SYDENSTRICKER..... 461
Experiments on the Filterability of the Granular Phase of the Tubercle Bacillus. RALPH R. MELLON AND ELIZABETH L. JOST..... 483
A Study of Pulmonary Tuberculosis in Children. A. LEVINSON..... 499
Tuberculous Cervical Adenitis. RICHARD H. MILLER AND WILLIAM M. SHEDDEN..... 511
Miliary Tuberculosis of the Lungs with Recovery. A Report of Two Cases. F. W. MARLOW, JR..... 529
The Graphic Method for the Blood-Sedimentation Test. Presentation of a 1-cc. Technique and Other Important Modifications and Suggestions. JACOB CUTLER..... 544
The Relationship Between Blood-Sedimentation Index and Fibrin Content in Tuberculous Individuals. ESTHER M. GREISHEIMER, CHARLOTTE C. VAN WINKLE AND OLGA H. JOHNSON..... 559

NUMBER 6, JUNE, 1929

Protective Inoculation Against Tuberculosis with BCG. A. CALMETTE AND HARRY PLOTZ..... 567
Coexistent Syphilis and Tuberculosis. ADOLPH L. GALLANT..... 573
A Unified Plan of Tuberculosis Control. BENJAMIN GOLDBERG..... 580
Obliterative Changes of the Pulmonary Lymph-Vessels in Tuberculosis. J. DWIGHT DAVIS..... 595
Reactions of the Subcutaneous Connective Tissue to Experimental Tuberculosis in the Guinea Pig. MAUDE L. LINDSEY..... 615
Observations on the Value of the Subcutaneous Tuberculin Test. G. D. KETTELKAMP..... 653
Dextrose in Synthetic Media for the Tubercle Bacillus. R. R. HENLEY..... 660
Exercise in Phthisis. I. RAPPAPORT..... 664

A NOTE ON LAENNEC'S INVENTION OF THE STETHOSCOPE

WARFIELD T. LONGCOPE

Many years ago in the old library of the Pennsylvania Hospital I happened to see a little book entitled *Sudden Death*, written by A. B. Granville and published in 1854. The title aroused my curiosity and a cursory glance through the book brought as a reward a few surprising paragraphs concerning the invention of the stethoscope. The main text is probably of little importance to-day, for it records in a very inadequate manner statistics on the incidence and cause of sudden death in England in the thirties and forties of the last century.

The preamble, however, has merit for it recounts the experiences of the author in the consulting rooms of many well-known physicians of the day. These consultations he sought for relief of symptoms simulating angina, which he feared might at any moment bring sudden death. Finally, he went to Laennec who, after a most careful examination assured him that his heart and lungs were normal, explained the origin of his symptoms and effected a complete cure. Granville was so much impressed by the care and accuracy of the examination that he forthwith made ward visits with Laennec, and it was during one of these visits that he presumes to have witnessed the actual invention of the stethoscope. The following extract contains the account of the episode:

At length hearing of the great and rising reputation of Dr. Laennec, in the treatment of diseases of the chest, at the Hôpital Necker, in which he had succeeded to the post of principal physician, on the death of Mongenot, which had taken place in 1815, I obtained admission into that hospital, through the Minister of the Interior, as a student, and for a time followed the professor's practice, waiting to see how his diagnoses were verified by dissections, before I again submitted my own case to the consideration of another French physician.

It was Laennec's habit, when examining a newly admitted patient, labouring under pectoral disorder, to percute him (as I have seen invariably done in the *Clinique of La Charité* also) in every part of the chest, both in front and at the back, as well as on either side. After which he would apply the ear to any

part which had resounded badly or imperfectly. One day (it was the 13th of September, 1816, for I took note of it) Laennec seemed dissatisfied with the result of his percussion and direct auscultation in an interesting but obscure case before him; when turning around to the circle of pupils around the bed, "Why," said he, "should we not avail ourselves of the help which acoustics yield to us, of making distant sounds more audible? The speaking-trumpet enables the dull of ear to hear the faintest whisper; the ascending tube in a warehouse conveys to the upper stories, in audible sounds, the muttered directions of the master below; the ticking of a watch placed at the end of a long beam, is heard loudly by the ear applied to the other extremity; a tube, therefore, applied over the lungs or to the chest over the heart, ought to instruct us more plainly through our ears, with the movements and sounds going on within;" and forthwith snatching the *cahier des visites* from the hands of the nearest *elève interne*, and rolling it up lengthwise to the shape of a cylinder, having a perforation through its axis he applied it first to one side of the chest, then to the other, and again to the back, between and below the shoulder blades, and declared (what we all know to be true) that he could make out with greater distinctness, than with the naked ear applied over the parts, their inward condition, from their respective sounds which he then described.

Such was the birth of that famous instrument, at first denominated by its inventor *pectoriloque*, which, slowly winning its way from the humble hospital, bearing the name of its founder, the unlucky minister of Louis XVI to every corner of Europe and to the new world, has laid open to the medical men in almost every instance, the scenes of disease enacted within the thorax, which before baffled detection. The invention of the stethoscope, simple and accidental as it may have been, marks a striking era in the history of medicine, and is second only in importance of results, to the discovery made by the immortal Harvey.*

On the following day Laennec had procured proper cylinders made of a thick pasteboard (to which he not long after substituted hard wood), eight inches long, and one and a half inches in diameter, perfectly smooth, with an even perforation in its center throughout its axis. It had the two ends somewhat hollowed out, so that the one which was applied to the convex parts of the chest, as well as the opposite end to which the ear of the examiner was applied, fitted admirably for both purposes. Such an instrument as this I brought to England in November, 1817 (that is, a year after its invention), when I first settled myself down in practice in Saville Row; and I well remember how most of my contemporaries, to whom the instrument was exhibited and explained, made themselves merry at the credulity of French doctors and my own.

* Why Laennec, in his first edition of the work, in which he announced the invention should have changed the scene of its first application from the ward of the hospital to the chamber of a fair patient, is not very intelligible to me, except on the score of French *gallanterie*. My own notes, taken down at the time and on the spot, are liable to no misconception.

SUDDEN DEATH.

BY

A. B. GRANVILLE, M.D., F.R.S.; M.R.C.P. (LOND.)

KNIGHT OF SEVERAL ORDERS; AUTHOR OF ST. PETERSBURG,
OR, A JOURNEY TO RUSSIA; THE SPAS OF GERMANY; THE SPAS OF ENGLAND;
KISSINGEN; TREATISE ON PRUSSIC ACID;
ETC., ETC., ETC.

ASSOCIATE OR CORRESPONDING MEMBER OF THE IMPERIAL AND ROYAL
ACADEMIES OF SCIENCES AND SOCIETIES OF PARIS, BERLIN, ST. PETERSBURG, BRUSSELS,
DRESDEN, BONN, TURIN, NAPLES, FLORENCE, VENICE, ETC.

LONDON:
JOHN CHURCHILL, NEW BURLINGTON STREET.
(*Established in Princes Street, Soho*, 1784.)
MDCCCLIV.

This description, which to my knowledge has never been referred to before, is at variance with the account which Laennec himself gives of the scene at which he invented the method, but it may be that the demonstration at the Hôpital Necker took place on a morning following the scene with the lady in the consulting room, and Laennec, arriving at the hospital enthusiastic about his new idea, might have demonstrated the invention to his students, without reference to the preliminary trial of the days before. Under any circumstances, the incident necessitates some further information about Dr. Granville, for this account, if correctly stated, adds an important date to the history of the stethoscope, and furnishes an interesting account of one of the earliest uses of the stethoscope in the wards of the hospital.

The little volume on sudden death is only one of several books which Granville wrote during a long and adventurous life. He published treatises on the plague, on obstetrics, on the use of hydrocyanic acid, on mummies, on travel in Russia, and on the spas of Germany and England. He wrote a *Catechism of Health* and a history of the Royal Society. But undoubtedly one of the most interesting volumes is an autobiography edited and published by his daughter, Paulina B. Granville, in 1874. In this he records in great detail a romantic and adventurous career.

Granville was born in Milan, Italy, on October 7, 1783, of Italian parents. His father's name was Carlo Bozzi, but his maternal grandmother had been an English woman by the name of Rosa Granville and when Dr. Granville, as a young man, took up his residence in England he adopted the English name of his grandmother. It would be impossible in a few paragraphs to give an adequate idea of the varied experiences which are described by the author of this autobiography, but a few words about his life and work and an indication of his character is excusable as a background to the story about Laennec. He writes in a manner to suggest a daily diary, and in fact he frequently refers to a diary as the basis of his book on sudden death.

As a boy he witnessed the occupation of Milan by General Bonaparte, studied at the University of Pavia from 1798 to 1802 under Spallanzani, Scarpa and Volta, escaped conscription, and later journeyed with William Richard Hamilton to Turkey under the title of Physician to the English Embassy at Constantinople. Arriving in Stamboul in 1803 he contracted the plague, but on recovery became family physician to a Greek household. In 1804 he obtained the appointment of second physician to the Turkish Fleet. While on a Mediterranean cruise in 1805

own case to the consideration of another French physician.

It was Laennec's habit, when examining a newly admitted patient, labouring under pectoral disorder, to percute him (as I had seen invariably done in the *Clinique of La Charité* also) in every part of the chest, both in front, and at the back, as well as on either side. After which he would apply the ear to any part which had resounded badly or imperfectly. One day (it was the 13th of September, 1816, for I took a note of it), Laennec seemed dissatised with the result of his percussion and direct auscultation, in an interesting but obscure case before him; when turning round to the circle of pupils around the bed, "Why," said he, "should we not avail ourselves of the help which acoustics yield to us, of making distant sounds more audible? The speaking-trumpet enables the dull of ear to hear the faintest whisper; the ascending tube in a warehouse conveys to the upper

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But, returning to our doings at the *Hôpital Necker*, some months passed in the daily employment of this new exploring instru-

he left the Turkish Navy and sailed to Malaga. Here an epidemic of yellow fever was raging, about which he makes some interesting observations.

The plague, of which he saw much in Constantinople, he describes as a contagious epidemic, being transmitted from person to person by direct contact; yellow fever, on the other hand, he describes as an infectious epidemic, by which he means that the disease is "influenced by locality and change of air" and is not communicable directly from one individual to another. He proceeds to cite cases in support of this view, and relates instances of patients suffering from yellow fever who moved to a healthy district without communicating the disease to persons with whom they came in intimate and daily contact.

He left Malaga for Gibraltar, where he arrived on the day of the battle of Trafalgar. He described life in Madrid and a journey to Lisbon, where in 1807 he obtained an appointment as acting assistant surgeon to H. M. S. Raven, an 18-gun sloop of war. For five years he served with the British Navy and then in 1813 settled in London and started practice.

During the next year, however, through his friendship with Mr. Hamilton who was then in the foreign office, he was sent on a semidiplomatic mission to Paris and Milan. On the journey he visited Volta, and in Geneva met Sir Humphry and Lady Davey and Mme. de Stael. In Paris he listened to Guy-Lussac lecture upon iodine and obtained through a letter of introduction a conference with the great Humboldt. In 1815 he returned to London and succeeded Dr. John Davey, the brother of Sir Humphry, as Lecturer in Chemistry in the Medical School of St. George's Hospital, "held at the old Hunter's Museum in Great Windmill Street." Here he was poisoned by chlorine gas which resulted in the illness that eventually led him again to Paris and to a consultation with Laennec.

In the autobiography, unfortunately, there is no mention of the consultation, nor any allusion to the stethoscope, and only once, somewhat later, does he refer to Laennec. In extenuation, to us, for these omissions, Granville states that it is not his intention in this autobiography to enter minutely into a description of his experiences in Paris, for "so many were the objects of my pursuits, so serious the combinations that followed, and so important the results obtained, that a separate volume alone could do justice to the subject." He goes on to say that he had prepared such a volume which was to be a "History of the State of Science in France during the revolution" but was dissuaded by "timorous"

friends from publishing it. In the four chapters devoted to his life in Paris he does mention attendance at the lectures of Cuvier, his study of obstetrics, a meeting with Pinel at La Salpétrière, the death of Mme. de Stael, and an introduction to Countess Rumford whose first husband was Lavoisier. Much later in the autobiography, however, the following reference to Laennec occurs: "Finding no pulse at the wrist, I applied my ear to the left side of her chest, as I had seen Laennec do at the Hôpital Necker in Paris, but I could hear no indication of any distinct movement," from which statement one wonders how profitable his visits to the Necker had really been.

In 1817 he returned to London, and with the advice and assistance of Sir Walter Farquhar began the practice of midwifery. Later he became editor of the London *Medical and Physical Journal.*

During this residence in London he busied himself in the affairs of several societies. For many years he acted as Secretary to the Board of Visitors of the Royal Institution of Great Britain. In 1825 he was active in promoting an obstetrical society, and made efforts to have the art of midwifery recognized as a legitimate branch of medical practice by the College of Physicians and the College of Surgeons. He next devoted his attention to the Royal Society of which he had been a Fellow for many years. Dissatisfied with the financial and scientific status of the society he endeavored to bring about reforms, and published an anonymous article on the subject entitled *Science without a Head.* One gathers that his criticisms for reform were far from acceptable to the other Fellows, and many stormy sessions must have followed the distribution of this article. In 1836, he published a book, *The Royal Society in the Nineteenth Century; being a statistical summary of its labours during the last 35 years with table, etc.*, but it was not until many years later that the suggestions which he made were adopted and practised to his satisfaction.

Granville was now over 50 years of age, but he continued an inveterate traveller. Twice he journeyed to Russia and once made a visit to the spas of Germany.

He tells of his professional and personal relationship with many persons of note while in practice in London and elsewhere. He saw Mrs. Siddons, the actress, Lady Pembroke, was the physician for many years to Lord Palmerston, while in St. Petersburg attended Princess Tczernicheff, the wife of the Russian Minister of War, and went in consultation to see the Grand Duke Michael, brother of Emperor Nicholas. For seven

years he was physician to those members of the Bonaparte family who resided in London, and devotes a chapter to his conversations with Joseph and Lucien, the brothers of Napoleon, and with Louis his nephew. He describes a banquet which he attended at Hanover Lodge, given by the Comte de Survilliers to most of the surviving members of the Bonaparte family and their friends.

He continued to practice, to travel, and to write until his eightieth year, and finally died on March 3, 1872, at the age of eighty-nine. The autobiography, though full of interesting observations and anecdotes, lacks literary merit and is surprisingly devoid of dramatic quality. His unusual experiences and adventures are recorded with little explanatory comment, and the material is presented with slight regard to the importance of the context. Insignificant conversations are quoted verbatim and at length, and long letters which contain little of general interest are reproduced, while matters of political or historical interest are dismissed in a few words. Granville evidently kept copious notes, and entered with meticulous care in a diary his daily activities. He set great store by the persons of quality with whom he came in contact, and pays somewhat more attention to titles than to subject matter. One can see, however, that he was concerned with detail, and his statements have all the quality of contemporary notes. Though he undoubtedly takes an unsophisticated pleasure in impressing his readers with the importance of his position in the world and with the exclusive society in which he lived, he reproduces his records in such a simple manner that they have all the signs of verity. It seems probable therefore that his description of the use of the stethoscope by Laennec at the Hôpital Necker is accurate, though the conclusion that he witnessed the invention of the instrument may be an indulgence to his childish vanity.

A STUDY OF BACILLUS CALMETTE-GUÉRIN (BCG)[1]

I. BIOLOGICAL CHARACTERISTICS, CULTURAL "DISSOCIATION" AND ANIMAL EXPERIMENTATION

S. A. PETROFF, ARNOLD BRANCH AND WILLIAM STEENKEN, JR.

Much interest and discussion have centered on the prophylactic immunization of children against tuberculosis as advocated by Calmette and his co-workers. The principle involved in the method is the vaccination of infants by feeding them living avirulent tubercle bacilli. Stress is laid on the fact that the vaccination must be done within the first ten days after birth. The literature on the subject is rapidly accumulating, most of it from the pen of the sponsors of the method, and is largely repetition.

The history of the microörganism dates from 1908 when it was isolated from a heifer, but its use for vaccination of infants was not begun until 1924. The claims of the authors are that this microörganism formerly had the characteristics of the bovine tubercle bacillus and was pathogenic for cattle, guinea pigs and rabbits at the time of isolation. However, after cultivating it repeatedly on a special medium, composed of potato slants treated with ox-bile and glycerol, the authors allege that a loss of pathogenicity resulted, though the microörganism still retained its immunizing properties. They at first stated that it did not produce anatomical tubercles but more recently they have modified their views, admitting that the anatomical tubercles are similar to those obtained with virulent microörganisms, varying only in the later behavior of the foci, which have a tendency to retrogress and in time to heal completely, without leaving a trace.

In a recent review, two of the authors (1) of the present studies presented a critical analysis of the statistical and the experimental data on this subject. In this review it was pointed out that the conclusions reached from animal experimentation were not sufficiently convincing. An examination of the statistical data in children also revealed that vaccinated and nonvaccinated control infants could not be compared fairly,

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

for the reason that the controls were not isolated from infection after birth, as were the vaccinated, an epidemiological factor of great importance. Such careless use of statistics afforded no aid in forming an opinion of the value of the vaccination. Recently Greenwood (2) and Rosenberg (3) have analyzed the figures presented by Calmette and have pointed out other gross errors which invalidated the results so far reported by the sponsors of the method; and they considered that no safe conclusion could be reached from the statistics published on these children.

Our interest in the microörganism dates from 1925 when in a small way we tested its virulence. Only two of eight animals inoculated with *BCG* at that time developed a progressive tuberculosis terminating in death. The inconstant findings led us to a further investigation, the results of which are incorporated in the present study.

In this paper only the cultural characteristics and pathogenicity of *BCG* for guinea pigs and rabbits are described; the immunity experiments will be presented in another publication.

EXPERIMENTAL DATA

Studies with the Original Cultures of BCG

The three cultures used in the following studies were received from different sources. The first was obtained from Dr. E. A. Watson of the Bureau of Animal Pathology, Ottawa, Canada, in the spring of 1925. It was a plain glycerol-egg slant of a few weeks' growth. In appearance it did not vary in any way from that observed in either human or bovine microörganisms, being dry and wrinkled. Upon its arrival subcultures were made on plain glycerol-egg medium for further use. The second culture was brought to us by Dr. Lawrason Brown in June, 1926, being given to him personally by Dr. Calmette. It was a glycerol-bile-potato culture, and the appearance of the growth was very moist and homogeneous. This original culture was subcultured both on glycerol-bile-potato and on plain egg media. The third microörganism studied was obtained directly from Dr. Calmette, who very kindly sent us in the spring of 1927 two culture-tubes of glycerol-bile potato upon which the microörganisms had been cultivated. One of the cultures was studied and the second was stored in the refrigerator for further use.

Cultural Characteristics on Various Media: The microörganism cultivated on plain glycerol-egg medium does not vary in essentials as to cultural characteristics from that of any other acid-fast microörganism. It is wrinkled and dry, chromogenic in spots, irregular, and waxy in ap-

pearance. It grows well on glycerol-gentian-violet, plain egg, glycerol-agar, veal-broth, Sauton's, and Proskauer and Beck's synthetic media. When cultivated on fluid media there is a period of lag lasting for a week or ten days, after which the growth spreads very rapidly from the original inoculum, continuing to expand until it covers the surface of the broth in the flask or bottle, and gradually making its way up on the sides of the flask. On careful examination of the surface growth, the pellicles are seen not to be uniform in structure, some being in masses with an occasional slightly chromogenic veil-like growth between. After several weeks the pellicles appear to be slightly moist in spots. This is followed by a gradual sinking of some of the growth to the bottom of the flask or bottle. From such a mature culture Old Tuberculin can be prepared, having physiological properties similar to that obtained from ordinary human or bovine tubercle bacilli. However, by a comparison of skin tests we found that this tuberculin was not as potent as that made from the human tubercle bacillus H37.

Morphology and Staining Reaction: The *BCG* is a slender, pleomorphic rod, 3 to 5 micra in length, some of the members having small granules which vary in size. It is gram-positive and acid-fast.

Development of Tuberculin Allergy in Animals Inoculated with BCG: Calmette (4) found that guinea pigs inoculated with *BCG* became skin-hypersensitive in about 15 days. Animals fed massive doses of the microörganism reacted with a positive skin test in 32 to 47 days. Calves inoculated subcutaneously, however, did not uniformly become allergic.

Tzekhnovitzer's (5) results with tuberculin tests of *BCG*-inoculated guinea pigs are not in agreement with those of Calmette. This author obtained only 70 per cent positive tuberculin reactions in animals fed with the microörganism and only 45 per cent positive reactions after subcutaneous inoculation. Furthermore, intraperitoneal and intracutaneous inoculations did not render the animals skin-hypersensitive. The intracutaneous reaction was elicited with Old Tuberculin and also with a tuberculin prepared from *BCG* cultures. Rabbits inoculated subcutaneously with the same microörganism became allergic, and the ophthalmic reaction was positive in 100 per cent, the intensity of the reaction being stronger with Old Tuberculin than with *BCG* tuberculin. In most instances the reactions, according to this author, were obtained two and one-half to four and one-half months after inoculation, much later than those obtained by Calmette.

Results of the Authors' Own Experiments: Our studies comprised

various methods of sensitization, with the object of comparing our results with those obtained by other workers.

The preparation of the suspension of living *BCG* for animal inoculation was as follows: A two-weeks' growth of the *BCG* microörganism, cultivated on Sauton's medium, was removed aseptically and triturated in a sterile mortar with a few drops of saline solution (pH 7.8). More saline solution was added from time to time during trituration. The suspension of the microörganism was removed with a sterile capillary pipette and put into a sterile test-tube, and there set aside for a short time to allow for sedimentation of the coarser particles. The strength of the supernatant milky suspension of microörganisms was determined by dry weight and the required strength made with saline solutions.

Subcutaneous Inoculations: These were made in four series. Only healthy animals not reacting to old tuberculin were used.

1: Ten guinea pigs were inoculated subcutaneously with 0.5 mgm.[2] four times at intervals of three days, a total amount of 2 mgm. One month later only three animals reacted definitely to 5 per cent Old Tuberculin; in the remainder the reactions were either questionable or negative. These animals were later used for immunity experiments.

2: Nine young guinea pigs, 36 hours old, were inoculated subcutaneously with 2.5 mgm. every second day on four different occasions. Three became positive to intracutaneous tuberculin on the 32nd day and the remainder were negative and were likewise used for immunity experiments.

3: Six adult guinea pigs received 7 to 14 mgm. by the same route, the inoculations being made on two occasions four days apart. All became positive to the intracutaneous test on the 70th day and remained so for five months. They are still under observation.

4: Twelve other guinea pigs were inoculated subcutaneously with a single dose varying from 1 to 8 mgm. Eleven gave a positive intracutaneous skin test on the 70th day and are still living five months later.

Intraperitoneal: Twelve animals were inoculated intraperitoneally with 0.5 mgm. on four occasions at three-day intervals. Nineteen days after the last inoculation all became positive to the intracutaneous test. These were used in immunity experiments. In another series of four animals, inoculated by the same route with only a single dose consisting of 2.5 mgm., three reacted positively in one month.

[2] Dry weights are used throughout. To compare these approximately with moist weights, as used by Calmette, multiply by 6.

Intratesticular: Of eight animals inoculated with 1 to 2.5 mgm. intratesticularly, four became positive in five weeks to two months. The infected testes of these animals were removed, triturated and inoculated in the same way into a series of 18 guinea pigs, eight of which developed skin hypersensitiveness. The reason for such a low percentage of positive skin reactions is that by repeated passage the number of living microörganisms in the infected tissue was so reduced that some of the animals did not receive a sufficiently large number of microörganisms to bring about an infection.

Peroral Sensitization: Ten young guinea pigs, 36 hours old or younger, were fed 0.7 mgm. with a pipette on four occasions every other day, a total amount of 2.8 mgm. The tuberculin skin test was negative in all of the animals three months after feeding. These animals were used for immunity experiments.

In another series four adult guinea pigs were fed a single dose of 15 mgm. Two became positive to tuberculin in 22 days. One died early in the experiment and the other never reacted. One of the animals which reacted positively to tuberculin died later of an undetermined cause, but an extensive lesion was present in the lungs. It showed itself as an area of brownish red, chronic consolidation involving the cephalic lobe. The central portion was caseous. Many acid-fast microörganisms were present and similar caseous lesions were found in the bronchial lymph nodes.

Koch's Phenomenon (Intracutaneous): Four guinea pigs were inoculated intraperitoneally with 2.5 mgm. of *BCG*. After sensitization two were inoculated intracutaneously with living *BCG* and two with a known human strain, H37. Three of the four animals reacted positively with local ulceration on reinoculation.

The foregoing experiments showed that intraperitoneal inoculation of *BCG* in 12 guinea pigs resulted in positive skin hypersensitiveness in 100 per cent. Of 37 guinea pigs, inoculated subcutaneously with various "doses" of the microörganism, 62 per cent reacted positively to tuberculin; of 26 animals inoculated intratesticularly 46 per cent became allergic; and only 2 of 14 guinea pigs, or 14.3 per cent, gave a positive tuberculin skin test after feeding with living *BCG* cultures.

Formation of Specific Antibodies in Rabbits' Blood. Four rabbits were inoculated intravenously with 2.5 mgm. of *BCG*. One month after inoculation the complement-fixation reaction became strongly positive to a heterologous glycerol antigen.

Another rabbit, which had been inoculated intraperitoneally with tuber-

culous tissue obtained from a *BCG* guinea pig, also gave positive complement fixation with heterologous glycerol antigen. The contact precipitin test with *Tubercumet*, a commercial preparation of tubercle bacilli similar to Zinsser's X-substance, however, was negative.

Two other rabbits inoculated intraperitoneally with 20, 10 and 10 mgm. of *BCG* at weekly intervals also reacted positively to the complement-fixation test.

In six other rabbits, two inoculated subcutaneously, two intraperitoneally and two intravenously, the complement-fixation test was positive to H37 glycerol antigen and also antigen prepared from *BCG*. These tests were repeated on several occasions, and the results were invariably positive.

From the preceding experiment, in which the inoculations were made intravenously, subcutaneously or intraperitoneally in 13 rabbits, the complement-fixing antibodies were not difficult to obtain. Precipitins, on the other hand, were demonstrated only in one rabbit.

Experiments on the Pathogenicity of BCG for Guinea Pigs and Rabbits

I: Watson's Strain (BCG I): A suspension of *BCG* in salt solution from a 14-day growth on glycerol-egg medium was prepared according to the method described elsewhere. It was diluted so that each cubic centimetre contained 20 mgm. of microörganisms (dry weight).

Eight guinea pigs, negative to the tuberculin skin test and weighing from 360 to 442 gm., were divided into four groups and inoculated subcutaneously in the groin, nos. 1 and 2 with 2 mgm., 3 and 4 with 4 mgm., 5 and 6 with 8 mgm., and 7 and 8 with 16 mgm. of the suspension. All the animals developed subcutaneous abscesses at the site of inoculation. The size of the abscess depended on the amount used. The intracutaneous skin test was strongly positive in each animal 50 days after the inoculation.

Eighty-four days after inoculation one animal from each group (nos. 1, 3, 5 and 7) was killed. All four had enlarged lymph nodes and spleens about twice normal size. In nos. 5 and 7 there was a number of definite macroscopic tubercles in the liver, and in no. 5 a few tubercles in the lungs. Acid-fast microörganisms were found in the lesions of all animals.

The remaining guinea pigs, nos. 2, 4, 6 and 8, were kept under observation. Number 4, which was inoculated with 4 mgm., died on the 165th day. At autopsy the inguinal lymph nodes were enlarged and caseous, and the spleen six times normal size and containing many tubercles. There were tubercles in the liver and in the lungs, while the bronchial

and cervical lymph nodes were enlarged and caseous. Acid-fast microorganisms were demonstrated in stained specimens of the tissue. Death in this animal was attributed to tuberculosis.

Guinea pig 8, which had been inoculated with 16 mgm. of the bacilli, died on the 196th day, with autopsy findings very similar to those described for no. 4.

On the 244th day the remaining animals, that is, no. 2 inoculated with 2 mgm. and no. 6 with 8 mgm., were tested with tuberculin. Both gave only doubtful reactions. At the site of inoculation there was a fibrous mass 2 mm. in diameter but no acid-fast microörganisms. The peritoneum was clear. In the liver there were some depressed areas, but no evidence of mascroscopic tubercles was found in the other viscera. The bronchial, cervical, inguinal and iliac lymph nodes appeared normal. There was no visible tuberculosis in either of these animals, and the infection was indicated by the positive tuberculin skin test done on the 50th day. At that time we could not explain the progressive infection and death of the two animals, nos. 4 and 8, which died from tuberculosis. There is no question that all the inoculated animals were infected by *BCG*, as this was shown from the autopsies in the four killed on the 84th day.

II. The First and Second Cultures Obtained from the Pasteur Institute: The preparation of the suspension of living microörganisms was similar to that used in the previous experiment.

Animal-Passage Inoculations: An attempt was made to raise the virulence of *BCG* by animal passage. Two small male guinea pigs, nos. 1 and 2, were inoculated in the right testis with 0.25 cc. of a heavy suspension of *BCG II*[3], prepared from one month's growth on glycerol-egg medium. Two weeks later the inoculated testis of animal no. 1 was removed and triturated in a mortar with sterile saline solution. This suspension was centrifugated at low speed, the supernatant fluid again centrifugated at high speed, and the sediment inoculated into the right testis of guinea pigs nos. 3 and 4. The skin test became positive in guinea pigs 3 and 4 on the 17th day, and remained so for nine weeks. At this time one of the subinoculated animals, no. 3, and one of the originals (no. 1 whose testis had been removed) were killed. Autopsy disclosed no macroscopic tuberculosis in no. 1, but the subinoculated animal, no. 3,

[3] This was the *BCG* culture brought to us by Dr. Lawrason Brown from the Pasteur Institute.

showed tubercles in the spleen as well as caseous inguinal and axillary lymph nodes.

A portion of the crushed lymph node from guinea pig 3 was emulsified, and cultivated on gentian-violet-egg plates according to a technique described elsewhere (6). The colonies obtained were later identified as possessing the typical "S" structure, which, as we shall see from the later studies, was the virulent microörganism present in the *BCG* cultures. The second portion from the diseased lymph node was again triturated and subinoculated subcutaneously into rabbit 1, which was used later in an immunity experiment, and also intravenously into rabbit no. 2. At the same time a guinea pig, no. 3A, was inoculated subcutaneously with the same material. This animal was killed on the 86th day after the inoculation. It showed progressive generalized tuberculosis. The suspected material was triturated and inoculated subcutaneously into another guinea pig, 3B, which died of generalized tuberculosis on the 137th day. Intraperitoneal inoculations with the diseased tissue of guinea pig 3B were also made into two other guinea pigs, 3C and 3D. These animals died of generalized tuberculosis on the 56th and 109th days respectively. Intraperitoneal inoculation of the tuberculous pus from the omentum of animal 3C was made into one rabbit, 3E, and intravenous inoculation into another rabbit, 3F. The intraperitoneally inoculated rabbit, 3E, was killed on the 80th day, when it showed a large caseous tuberculous mass in the omentum. The "intravenous animal," 3F, became crippled and moribund, and was therefore killed on the 257th day. Widespread tuberculosis of the joints of both extremities, with abscesses containing many acid-fast microörganisms, was found. There were some healed tubercles in the kidney, tuberculous pyelitis and one caseous mass in the lungs. (See plate 7.)

Autopsy of Rabbit 3F: Lungs: In the left cephalic lobe an 8-mm. emphysematous bleb surrounded by a zone of chronic consolidation. No other lesions. *Spleen:* x 1, dull and dry. *Liver:* Large and firm; dark purple with some grayish areas of infiltration. *Kidneys:* Large and dark. Surface spotted with large, slightly depressed, irregular pittings showing little cicatrization; pelves full of thick caseous material; on section two 1-mm. caseous tubercles in cortex of one kidney. *Bladder:* Contracted and empty. *Head* and *Spine:* No lesion. *Shoulder* and *Hip Joints:* Intact. *Other Joints:* Lesions as follows: *Right Fore Leg:* Elbow joint intact; wrist joint very swollen, due to yellow caseous abscesses, thin-walled on all sides, which fluctuated and exuded thick white pus on section. The swelling extended downward over the metacarpals and first

phalanges, chiefly over the dorsal aspect but also on the ventral. Some of the abscesses were separately walled off from others. *Left Fore Leg:* Elbow joint intact. There was a similar but less marked swelling around the wrist joint which measured 4.75 cm. after the skin was removed. There were localized encapsulated abscesses, extending for 1 cm. on the radial side and 2 cm. on the ulnar. The rest of the swelling was entirely on the ventral side extending over the metacarpals. *Right Hind Leg:* On ventral surface of third metatarsal bone and its phalanges, a series of small localized caseous abscesses. *Left Hind Leg: Ankle:* Large caseous abscess over outer malleolus, extending in front of it, and measuring 12 cm. in circumference. Smaller abscess anterior to inner malleolus. On ventral side larger abscess, extending along between third and fourth metatarsals. At fourth metatarsophalangeal joint another 6-mm. caseous abscess on dorsal aspect, and extending along metatarsal bone. An abscess 3 mm. in diameter was situated on the fibular side of the joint between the second and proximal phalanges of the third toe.
Smears: Abscess Right Wrist Joint: Gram stain,—no microörganisms. Ziehl-Neelsen stain,—many acid-fasts. *Pus from Kidney-Pelvis:* Many acid-fasts. *Bone-Marrow from Femur:* Many acid-fasts.
Microscopic: Liver and Spleen: No tubercles. *Lungs:* Mononuclear and caseous tubercles with giant cells. Many acid-fast microörganisms present. *Kidney:* Scars in cortex; cellular exudate of mostly mononuclear lymphocytes under epithelium of pelvis.
Cultures: These were made from the pus of the right wrist joint on several gentian-violet-egg plates. Twenty days later a growth appeared on one plate. This was removed, triturated with saline solution, and inoculated intravenously into two rabbits, nos. 1 and 2, which are still living three months after the inoculation.

Some of the animals from this intratesticular passage experiment were killed at various intervals. Localized caseous lesions containing acid-fast microörganisms persisted in the testis or the scrotum for 87, 140 and 236 days after the inoculation, but they never progressed. At the end of the seventh month from the beginning of the experiment the animals were again inoculated subcutaneously with 1 mgm. *BCG.* This second inoculation was again followed by lesions at the site of inoculation which persisted as long as 152 days. The guinea pigs that survived were transferred to an immunity experiment.

Parallel with the foregoing experiment, control testicular inoculations were made as follows: Heat-killed tubercle bacilli, H37, were injected into the right testes of two animals. Several weeks later the inoculated testes were removed, triturated, and inoculated similarly into two other

healthy animals. This procedure was carried for one more passage, a total of 6 animals being used. Similar inoculations were made with an avirulent living human strain, R1. Six passages were made, each consisting of 2 guinea pigs, or a total of 12. The object of these control inoculations was to see whether progressive tuberculosis could be obtained by a chance contamination with bacilli other than the one employed. In no instance did progressive tuberculosis occur in these two groups which were carried through three and six passages respectively. This strengthens our belief that the technique employed was not faulty and that the progressive disease seen in animals inoculated with *BCG* was not due to an outside contamination, but to the virulent microörganisms present in the original *BCG* culture. Some of our critics have suggested such contamination.

Direct Subcutaneous Inoculation: Nineteen healthy guinea pigs giving a negative skin test to tuberculin were inoculated subcutaneously with a suspension of *BCGIII*[4] culture, the dosage varying from 1 to 10 mgm. Within a few weeks nodules appeared at the site of inoculation. In the animals receiving large dosage subcutaneous abscesses appeared which later ruptured and completely healed in two to four months. In many of the animals enlargement of the lymph nodes also occurred and disappeared in about the same length of time. Two weeks after the primary inoculation the animals were divided into three groups.

Group I: (9 guinea pigs): These animals received only the primary inoculation mentioned above. Animal 1 in this group died of an undetermined cause on the 126th day. At autopsy there were tubercles found at the site of inoculation and tuberculous abscesses were present in the omentum. These were triturated and inoculated subcutaneously into two other healthy guinea pigs, both of which are still living on the 77th day. Guinea pig 2 died on the 134th day of a streptococcus abscess of the neck and the spleen. Acid-fast microörganisms were found only at the site of inoculation. The other organs were normal. Guinea pig 3 was killed on the 148th day. The inguinal lymph nodes were very much enlarged and caseous. Acid-fast microörganisms were present but there was no other evidence of tuberculosis. Guinea pig 4 died on the 207th day. The lymph nodes were very much enlarged and caseous and contained many acid-fast microörganisms. There were also tubercles in the spleen. The lungs and liver were apparently normal. Guinea

[4] This was one of the cultures received directly from Dr. Calmette in the spring of 1927.

pigs 5 and 6 died on the 212th day. The cause of death of animal no. 5 could not be determined. The inguinal lymph nodes were very much enlarged and caseous, containing many acid-fast microörganisms. A few tubercles were present in the spleen and liver. In animal no. 6 the inguinal lymph nodes were slightly enlarged. There were many tubercles in the spleen and liver. The cervical and bronchial lymph nodes were very much enlarged and caseous. In all probability this animal died of tuberculosis. Guinea pigs 7, 8 and 9 are still alive on the 212th day.

Group II consisted of 6 guinea pigs, nos. 10, 11, 12, 13, 14 and 15. Two weeks after the primary inoculation a second subcutaneous inoculation was made, consisting of 15 mgm. of a fresh suspension of the same microorganism. All developed large subcutaneous abscesses which ruptured and healed in 2 to 4 months. Two of these 6 guinea pigs developed palpable lymph nodes which disappeared in about the same length of time. Microscopically there were some mononuclear tubercles with giant cells in the regional lymph nodes of animal no. 10 which was killed 100 days after the first inoculation. The other 5 animals are still alive after 6 months.

Group III consisted of 4 guinea pigs, nos. 16, 17, 18 and 19, which were reinoculated 10 weeks after the primary inoculation with 1.5 mgm. of a fresh culture of living *BCG III*, nos. 16 and 17 intraperitoneally and nos. 18 and 19 intratesticularly. Nineteen days later animal no. 16 was killed. There were microscopic tubercles in the omentum, peritoneum and spleen. The remaining three animals are still living six months after the inoculation.

In another series four guinea pigs, nos. 20, 21, 22 and 23, were inoculated subcutaneously with 6 mgm. of the microörganism, and 28 days later they were again inoculated intracardially with 2.5 mgm. of a pure culture. Three of the four animals died within 3 days of postallergic collapse. At autopsy there was a subcutaneous abscess at the site of inoculation containing many acid-fast microörganisms, the lymph nodes were congested, there was necrosis of the spleen, and macroscopic tubercles in the lungs were confirmed histologically. Animal no. 23 is still living 10 weeks after the intracardiac inoculation.

Peroral: Four guinea pigs were fed a suspension of 15 mgm. of *BCG* with a pipette. One died in 2 days from *B. Friedländer* pneumonia. Numerous acid-fast microörganisms were found in the lungs, probably due to inspiration during the feeding. The second animal died of otitis in 32 days with no macroscopic lesions. The third died in two months

with a large caseous focus in the lungs and very much enlarged caseous bronchial lymph nodes. Acid-fast microörganisms were demonstrated. The fourth died in 112 days of an undetermined cause. Histologically there was local fibroid tuberculosis in the lungs.

The preceding experiment on the pathogenicity of the original cultures, that is, the Watson strain (*BCGI*), *BCGII* and *III*, which were obtained from the Pasteur Institute, may be summarized as follows:

1: We are in agreement with others that *BCG*, under cultivation either on glycerol-bile-potato or on Sauton's medium, is, as a rule, innocuous when inoculated into guinea pigs and rabbits; that tuberculous changes do take place after the microörganism enters the body and that the lesions have a tendency to heal.

2: Progressive tuberculosis, leading to the death of the guinea pig, occurred in 2 out of 8 animals inoculated with Watson's *BCG I*. In the testicular passage experiment, in which 18 animals were inoculated with *BCG II*, only one developed progressive tuberculosis. The lesions from this animal produced progressive tuberculosis by passing them from animal to animal in a series of five passages. When direct inoculations of *BCG III* were made in 23 animals, tuberculous changes were found in four, but the cause of death was attributed to tuberculosis in only one of these animals. In peroral inoculations only one of the animals had tuberculous changes of nonprogressive type.

It was obvious from these experiments that we were dealing with cultures which contained both virulent and avirulent microörganisms. Ordinarily, suspensions of the various cultures investigated contained the two forms, the avirulent microörganism outnumbering the virulent. Most of the animals inoculated with such suspensions naturally received the avirulent microörganism and escaped the virulent strain, but occasionally, when an animal was inoculated with the virulent microörganism, progressive disease developed.

The inconstancy in the virulence of this microörganism, as shown by the various studies so far reported, was very puzzling. Was a spontaneous tuberculous infection the cause of death in the animals dying from tuberculosis?[5] We are certain that even some of the partisans of this method of vaccination have had results similar to ours, but the occasional generalized tuberculosis seen was attributed (1) to a spontaneous tuberculous infection in guinea pigs and (2) to accidental laboratory contami-

[5] The authors believe that spontaneous tuberculosis is an extremely rare occurrence in guinea pigs.

nation with virulent tubercle bacilli and not to a virulent microörganism present in the *BCG* culture.

Calmette's accusation in regard to Nobel's and our own experiments of the possibility of contamination with a virulent tubercle bacillus is not justifiable. A careful survey of the technique rules out the possibility of such contamination. As nearly as possible an aseptic bacteriological technique was followed throughout all inoculations. Mortars, pestles and all glassware were treated with chromic acid and dry-sterilized at 150° C. for one hour. While no contamination was possible, in our judgment, there was yet a chance that another explanation would be found. Hence, the following investigation was undertaken with the hope that it might explain the variation in the virulence of *BCG* observed not only by us but by other investigators as well.

The Dissociation of BCG

During the cultivation of *BCG* on Sauton's medium we had noticed, as mentioned before, that there were small islands, raised and wrinkled, with a rather more or less veil-like pellicle surrounding them. These small islands predominated, but in some parts of the flask there was a spreading growth that appeared slightly yellowish and moist on the surface. This observation suggested the possibility of the existence of two different microörganisms in the same culture, which by the use of the newer methods applied in bacteriology might be separated and thus studied.

From the recent studies on microbic dissociation (7) we now know that in practically all pathogenic microörganisms, when under cultivation outside the body on suitable media, there are present two types of microorganisms that differ not only in structure and formation of colony but in certain biological properties. One of these types has been designated as "*S*"[6] and is pathogenic for animals, while the other, called "*R*,"[6] is nonpathogenic or only slightly pathogenic. Therefore, we concentrated our attention on the problem of dissociating the tubercle bacillus, and especially *BCG*, into virulent "S" and avirulent "R" colonies. After many trials the following method proved successful and a great aid in dissociation studies (6).

[6] The nomenclature used in microbic dissociation at present is not very satisfactory. *S* designates smooth and *R* rough colonies as applied to other microörganisms. It is advisable to use these letters at present, but interpret them as suggested by Hadley (7); that is, *S* meaning sensitive and *R* resistant to environment.

Method: A small portion of the growth from synthetic fluid cultures was removed, and triturated in a test-tube with salt solution having a pH of 7.8. The suspension was filtered through two layers of Whatman paper no. 5, and the clear filtrate inoculated on the surface of egg medium containing gentian-violet (1–20,000) and made up in petri dishes. Rubber bands were put over the edge of the plates to prevent contaminations and dehydration. The plates were incubated in the usual way. At the end of 48 days single colonies appeared on the plates, the majority of them being of uniform structural characteristics. However, there were a few scattered colonies differing in certain respects, which we shall describe in detail later.

Inspection with a hand lens rendered it possible to select the two different colonies, which were removed and triturated separately, and filtered as before through two layers of Whatman paper no. 5. Five drops of each suspension were inoculated on the surface of fresh gentian-violet-egg plates, sealed with rubber bands, and incubated as usual. After several repetitions we finally obtained pure cultures of two distinct colonies.

Description of the "R" Colony

It can be seen from plate I, figures 1 and 2, that the "R" and "S" colonies have distinctly different cultural characteristics. Colony "R" is very waxy, with large raised folds that are smooth on the surface. These folds start from the centre of the colony and run toward the periphery. The centre, in very young colonies, is creamy in color but as the colonies age it becomes a light orange color, and then darker as the colonies get still older. The periphery is clean cut, rounded, and slightly raised, and does not extend into the medium (plate I, figure 2). This colony is very difficult to emulsify in salt solution of pH 7.2.

The staining reaction of the individual bacilli does not vary noticeably from that of other acid-fast microörganisms. Morphologically the rods are not very long and the majority are beaded. They grow well on glycerol-beef-broth and on Sauton's fluid medium, but multiply with difficulty in alkaline synthetic medium. It must be remembered that the reaction of the Sauton medium is pH 7.0–7.2, while that of Proskauer and Beck's synthetic medium (8) is around 7.4–7.6. The former is not as well buffered as the latter. If an attempt is made to cultivate this colony continuously on Proskauer and Beck's synthetic medium, no growth will take place after the second or third subcultures. The most suitable for a favorable propagation of this colony appears to be Sauton's medium with a pH of 6.4. There is a usual lag of about seven days, after

which the surface of the broth becomes pretty well covered with the small islands which are uniform in size (see plate II, figure 1). This surface growth is heavy and raised, and the pellicles are wrinkled; the particles are not very coherent, and are easily removed without dragging along the whole floating mass. The growth is also difficult to prepare in a finely divided even suspension in saline solution having a pH of 7.2.

If a filtered suspension of the "R" colony is cultivated on slices of glycerol-bile-potato in petri dishes,[7] the colonies first appear as small round pebbles, the surface of which is perfectly smooth (plate II, figures 3a and 4a), gradually increasing in size and reaching from 1 to 2 mm. in diameter (plate II, figure 4b). The surface of this colony remains perfectly smooth for the first month. After four to six weeks a small granular papilla appears at the end of the smooth colony (plate II, figure 3f). Gradually this secondary growth covers the surface of the colony (plate II, figures 3c and 4c). At the second or third month several shoots of secondary papillae develop (plate II, figure 4d), which are very coarse and granular in appearance. Eventually the original colony becomes replaced by an entirely new structure (plate II, figures 4e).

At the first and second stages of development, when the colony is perfectly smooth, the microörganisms are very readily emulsified, but at the later stage it is almost impossible to emulsify them entirely. We have not as yet completely studied these successive cycles in the development of the "R" colony when cultivated on glycerol-bile-potato.

Pathogenicity of the "R" Colony

Guinea Pigs: Subcutaneous Inoculation: Ten guniea pigs were inoculated subcutaneously with 2 mgm. of a *BCG* "R" colony. One month later 6 of the 10 animals showed large nodules at the site of inoculation. These increased in size, forming abscesses which in time ruptured and discharged caseous pus containing tubercle bacilli. In these 6 animals the inguinal lymph nodes could be palpated, as they were of fairly good size. However, after one to three months all decreased in size and the

[7] The glycerol-bile-potato can be prepared in plates giving a large surface which is of great advantage in studying single colonies. Large potatoes are cut in round discs, 6 to 8 mm. in diameter and 3 mm. thick. They are treated by Calmette's method (9) and sterilized in a beaker, transferred to sterile petri plates aseptically, and a small amount of glycerol-bile is added to prevent evaporation. Rubber bands are put around the plates, as described in the preparation of gentian-violet-egg, and they are incubated to test their sterility, after which they are ready for use.

induration practically disappeared. The animals were then transferred to a *BCG* immunity experiment.

In another series 2 guinea pigs, inoculated similarly to those described above, were allowed to live for 328 days. At autopsy neither showed any pathological changes. Two other guinea pigs, inoculated more recently by the same route with 2.5 mgm, are still alive after four months.

Intracardiac Inoculation: Three guinea pigs were inoculated in the left ventricle of the heart with 1.25 to 2 mgm. of the "R" colony. One died of an intercurrent disease in 30 days with no macroscopic evidence of tuberculosis. The second died in 266 days of a tuberculin allergic reaction following a skin test; there was well-marked tuberculosis in the liver and spleen. The diseased tissue from this animal was triturated and inoculated into a second guinea pig, which was killed four months later, revealing no tuberculosis. The third died on the 375th day with extensive tuberculosis (plate V, figure 2). Contrary to our expectations, progressive tuberculosis was the result of this inoculation with the "R" colony, and the result may be contradictory to the statement which is made throughout this paper that the "R" colony is nonpathogenic. We shall later offer a possible explanation of the occasional occurrence of a progressive disease when this type of colony is used for inoculation. The diseased tissue from this animal was triturated and inoculated into a guinea pig, which died 41 days later of pneumococcus pneumonia and with only localized tuberculosis in the regional lymph nodes.

Intratesticular Inoculation: Following the inoculation of 2.5 mgm. of "R" colony into the right testis of two gunea pigs, enlargement of the regional lymph nodes resulted. When the animals were killed on the 51st and 75th day respectively, there was definite tuberculosis in the spleens, inguinal and iliac lymph nodes, as well as in the testes.

Intraocular Inoculation: A suspension of 0.25 mgm. of "R" colony was inoculated into the vitreous humor and anterior chamber of the right eye of three guinea pigs. One died after 76 days of gastroenteritis, and a tuberculous lesion was found only in the inoculated right eye. The remaining animals, after negative tuberculin skin tests, were killed on the 348th day. No lesions of the viscera could be found, and the only evidence of tuberculosis was that present in the inoculated eye which had atrophied and become fibrous.

Rabbits: Intraocular Inoculation: Two rabbits were inoculated in the anterior chamber of the right eye with 0.1 mgm. of "R" colony in suspension. The first was killed on the 86th day. There were no lesions in

the viscera but complete destruction of the eye had taken place. The second rabbit died of pneumococcus pneumonia on the 156th day. The only evidence of tuberculosis was in the inoculated eye, which had atrophied.

Intracardiac Inoculation: Two rabbits were inoculated in the left ventricle of the heart with 8 mgm. of "R" colony in suspension. One killed on the 87th day showed no tuberculosis. The other presented no evidence of tuberculosis after five months and was transferred to a *BCG* immunity experiment.

Intravenous Inoculation: Another series of 6 rabbits was first vaccinated with a suspension of heat-killed "R" colony. The object was incidentally to produce an anti-"R" serum in the animals. They were then given 2.5 and 5 mgm. of living "R" in suspension intravenously. All were well at the end of six months.

Intraspinal Inoculation: Two rabbits were inoculated with 0.16 mgm. of "R" colony in suspension. One died in 20 days of postpartum infection. Acid-fast microörganisms could be found in the spinal fluids. The other appeared well after the fifth month and was used in an immunity experiment.

Description of the "S" Colony

The cultural characteristics of the "S" colony (plate I, figure 1) on gentian-violet-egg medium differ from those of the "R" colony. There are many small irregular wrinkles, which are not smooth, as in "R", and do not appear waxy. The centre is considerably raised, gradually declining toward the periphery. The periphery is irregular, sometimes extending into the medium. On the whole, the growth appears honeycombed. Morphologically, the bacillus of the "S" colony is a slender acid-fast rod; granules are not so common as with "R." The bacilli are much more readily emulsified in salt solution of pH 7 – 7.2. They grow well on glycerol-beef-broth, Sauton's, and synthetic media, and are not sensitive to acid or alkaline reactions of the media. The maximum growth seems to take place in a medium having a pH of 7.6. When a comparison is made of the growth on fluid media having a pH of 6.4 with that on media of pH 7.4, the amount is almost double in the latter instance. The period of lag is very sort. If an attempt is made to cultivate this colony on glycerol-bile-potato medium, no visible colonies appear. However, scrapings made from the surface of a 26-day bile-

potato plate and inoculated subcutaneously into a guinea pig, and a small portion also planted on the surface of several gentian-violet-egg plates, revealed that the microörganism was still viable. The animal died in 15 days from an intercurrent disease but showed a tuberculous lesion in the regional lymph nodes. Normal growth took place on the gentain-violet-egg plates and was inoculated subcutaneously into two healthy guinea pigs, one of which died in 36 days with localized tuberculosis and the other in 152 days from generalized tuberculosis. Scrapings made on the 41st day from another bile-potato plate were inoculated on the surface of gentian-violet-egg plates, and inoculated subcutaneously into two guinea pigs. One animal, killed at the tenth month, showed local abscesses at the site of inoculation and enlarged lymph nodes. Tuberculosis was present in the inguinal and iliac lymph nodes and in the spleen and there were a few tubercles in the liver and in the lungs. There were eight colonies on one of the gentian-violet-egg plates inoculated with scrapings and 25 colonies on the other plate. Their cultural characteristics were similar to those of the "S" colony. The results indicated that although there were no macroscopic "S" colonies on the glycerol-bile-potato, the microorganism had remained viable and capable of causing infection in guinea pigs.

Pathogenicity of the "S" Colony

Guinea Pigs: Subcutaneous Inoculation: Twelve animals were used and divided into four groups.

Group I: Four were inoculated with 0.25 mgm. (dry weight); the first death occurred on the 51st day and was due to otitis. Tuberculous changes were present at the site of inoculation, and in the spleen, liver and lungs. However, the process was not very extensive. The second animal died on the 103rd day from generalized tuberculosis, and the third on the 105th day from otitis and tuberculosis of the lymph nodes, liver and lungs. The fourth animal is still living ten months after the inoculation.

Group II: Four received 0.5 mgm. One died on the 21st day of otitis and tuberculosis of the omentum, lymph nodes, spleen and liver (degree ++). The second animal died on the 103rd day and the findings were similar to those in the preceding animal. The third animal died in 151 days of generalized tuberculosis. The fourth is still alive ten months after the inoculation.

Group III: Two animals were inoculated with 1 mgm. The first died in 33 days and the cause of death was undetermined. There was tuberculosis in the omentum, liver, spleen, lungs and kidney. The second died in 103 days of generalized tuberculosis.

Group IV: Two guinea pigs were inoculated with 2 mgm. The first died in 34 days of an unknown cause, but tuberculosis was present at the site of inoculation, and in the lymph nodes, spleen and liver. The second animal died in 119 days of generalized tuberculosis. *First Passage:* The diseased tissues from the first animal in group IV were triturated and inoculated subcutaneously into a normal guinea pig, which was killed on the 40th day. There were tubercles at the site of inoculation and in the lymph nodes, spleen, liver, and lungs. *Second Passage:* The diseased tissues from this subinoculated animal were triturated and reinoculated subcutaneously into two other healthy guinea pigs, one of which died in 118 days of generalized tuberculosis. The other was killed on the 262nd day, and there was generalized tuberculosis of the lymph nodes, spleen, liver and lungs.

Intracardiac Inoculation: Left ventricular inoculations were made into three guinea pigs, in amounts of from 1.25 to 2 mgm. of "S" colony suspension. The first animal died from snuffles in 26 days; generalized tuberculosis was present. The second died in 27 days of generalized tuberculosis, and the third was killed, when moribund, on the 36th day, and at autopsy showed generalized tuberculosis.

Intratesticular Inoculations: These were made into two animals with 1.25 mgm. of "S" colony. One was killed on the 51st day, and at autopsy showed generalized tuberculosis. The second died on the 75th day of generalized tuberculosis. Subinoculations were made intraperitoneally into two healthy guinea pigs, one of which died in 60 days with tuberculous peritonitis and generalized tuberculosis. The second died in 256 days with otitis and tuberculosis of the lymph nodes, spleen, omentum, lungs and liver (degree ++).

Intraocular Inoculation: Three guinea pigs were inoculated in the vitreous humor and right anterior chamber with from 0.2 to 0.25 mgm. of "S" colony. One died on the 42nd day of generalized tuberculosis and tuberculous peritonitis (plate VI, figure 2). The second animal died on the 76th day and the third on the 91st day, both of generalized tuberculosis.

Rabbits: Intraocular Inoculation: Two rabbits were inoculated in the anterior chamber with 0.1 mgm. of the same suspension. One was killed on the 86th day and the other was allowed to live. Both animals had caseous lesions in the right eye, which eventually healed, but the eye was completely involved.

Intracardiac Inoculation: Two rabbits were inoculated intracardially with 0.8 mgm. of "S" colony. One was killed on the 87th day and showed tuberculous pyelitis, many tubercles in the kidney, and a few in

the lungs and in the pericardium. The other, killed on the 86th day, showed tubercles only in the kidney. The suspected material from the last animal was triturated and reinoculated intracardially into one rabbit, which is still living after ten months.

Intravenous Inoculation: Five rabbits were first sensitized with a heavy suspension of heat-killed "S" colony with the object of producing an anti-"S" serum. One month later intravenous inoculations were made with a suspension of living "S" colony, the dosage varying from 2.5 to 5 mgm. The first animal died on the 73rd day of an undetermined cause; only a few tubercles were found in the left lung. There were no other pathological changes. The second animal died on the 106th day, and tubercles were found in the lungs and kidneys (plate VI, figure 1a). The lymph nodes were also very much enlarged. The suspected lesions were triturated and inoculated subcutaneously into a healthy rabbit which is still living (one month). The third animal was reinoculated with a suspension of living "S" colony, and killed on the 66th day. Large caseous tubercles were seen in the caudal lobes of both lungs and there were also tubercles in the kidneys (plate VI, figure 1b). The fourth and fifth rabbits are still living and are apparently well.

Two other normal rabbits were inoculated intravenously with 5 mgm. of a suspension. One died on the 25th day of oedema of the lungs. There were acid-fasts in the bone-marrow, but no other visible lesions. The second animal is alive three months after the inoculation. Two other animals were inoculated intravenously with a similar dose. One died of inanition on the 83rd day, without evidence of tuberculosis. The other is still alive after five months, and was transferred to an immunity experiment.

Intraspinal Inoculation: Two rabbits were inoculated intraspinally with 0.16 mgm. of "S" colony in suspension. After five months, there being no clinical evidence of tuberculosis, these also were transferred to the same immunity experiment.

Histological Study of Inoculated Animals

Pathological Examination

The Undissociated BCG Strain: The earliest lesion studied, apart from the local subcutaneous lesions which produce typical tubercles and caseation, was in an adult guinea pig which died of an undetermined cause two months after being fed from a pipette with 1 cc. of a 15-mgm. suspen-

sion of *BCG*. At autopsy a large caseous focus, surrounded by a zone of chronic consolidation, was found in the cephalic lobe of the left lung. The bronchial lymph nodes were enlarged and showed caseous foci. Acid-fast microörganisms were found in both sites. Microscopically, the lung showed a large central necrotic area walled off by mononuclear cells and fibrous tissue. The bronchial lymph nodes showed many small caseous abscesses and mononuclear tubercles.

In another animal, inoculated subcutaneously with 1 mgm., histological tubercles consisting of mononuclear and giant cells were found 126 days later at the site of inoculation. The regional lymph nodes in another animal showed definite mononuclear tubercles 100 days after subcutaneous inoculation with 10 mgm. Another animal given the same dose showed fibrous tubercles with necrotic centres on the 148th day. Persistence of gross lesions for a longer period has already been noted.

Caseation was more prone to occur in the reinfected animals, and the necrotic regions seen in the spleen in fulminating tuberculosis in the guinea pig followed intracardiac reinoculation. Two animals, which died of an allergic reaction three days after intracardiac reinoculation of 2.5 mgm. subsequent to a subcutaneous inoculation of 3 mgm. 28 days previously, showed necrotic foci in the spleen, caseous tubercles in the lungs and mononuclear tubercles in the liver.

Another animal, which was killed 19 days after intraperitoneal reinoculation of 1.5 mgm. subsequent to a subcutaneous inoculation of 8 mgm. eleven weeks previously, showed caseous tubercles in the liver and omentum and mononuclear tubercles, with giant cells, in the spleen.

The Dissociated Colony "R": Intraspinal inoculation of 0.4 mgm. produced mononuclear tubercles in guinea pigs dying 20 and 30 days later.

An animal, killed 51 days after intratesticular inoculation of 1.25 mgm., showed mononuclear and caseous tubercles with abscesses in the inguinal lymph nodes, and another killed in 75 days showed mononuclear tubercles with caseation in the spleen. In an animal, killed 76 days after inoculation of 0.2 mgm. in the anterior chamber of the eye, there were caseous mononuclear tubercles. Atrophy of the eye persisted until death in both guinea pigs and rabbits.

One animal, which died following a tuberculin skin test 266 days after intracardiac inoculation of 2 mgm., showed mononuclear and caseous tubercles, with giant cells in the spleen and periportal fibrosis in the liver. Another, killed 375 days after intracardiac inoculation of 1.25 mgm.,

showed mononuclear caseous tubercles in the spleen, periportal fibrosis in the liver, and mononuclear fibrous tubercles in the lungs.

Colony "S": Intraspinal inoculation of 0.4 mgm. into guinea pigs produced mononuclear perivascular tubercles in the meninges in 19 days. Intracardiac inoculation of 1.25 mgm. into guinea pigs produced mononuclear tubercles in the lymph nodes and spleen and necrotic foci and periportal infiltration in the liver after 16 days and similar changes in 26 days. After intratesticular inoculation of 1.25 mgm. two animals showed generalized lesions in 51 and 75 days, that is, tuberculous necroses and areas in the spleen, and mononuclear tubercles in the lymph nodes, lungs and liver. Mononuclear tubercles were found in the eyes of two guinea pigs and two rabbits 76 and 86 days after inoculation with 0.1—0.2 mgm. Atrophy of the eyes was complete, and in the guinea pigs generalized tuberculosis followed. After the subcutaneous inoculation of 2 mgm. into guinea pigs generalized tuberculosis was found from 34 to 119 days later. Intracardiac inoculation of 0.8 mgm. in rabbits killed in 87 days showed mononuclear tubercles in the lungs, tuberculous pyelitis, and mononuclear tubercles in the kidneys.

Two rabbits sensitized with dead "S" microörganisms, and inoculated intravenously later with 2.5 and 5 mgm. of living "S" showed caseous encapsulated tubercles in the lungs and kidneys 66 and 106 days after the last inoculation with living microörganisms.

The virulent strain obtained from a guinea-pig passage (intratesticular inoculation) produced generalized tuberculosis in successive guinea pigs, and one rabbit, killed after 256 days, showed bone and joint tuberculosis, tuberculous pyelitis, and tubercles in the kidney (see plate VII).

Summary of Pathological Findings

The original (undissociated) culture and the "R" colony, when inoculated subcutaneously, produced typical tubercles in guinea pigs and in rabbits; the lesions in many did not progress, but remained localized and eventually healed. Fibrosis was not uncommon in the lesions studied. The intracardiac inoculation, made with the original culture or the "R" colony, sometimes resulted in generalized tuberculosis in guinea pigs. By passing the original culture from one animal to another, the virulence could be regained, and it produced progressive lesions. However, the "S" colony and the microörganism isolated from passage animals often

produced generalized tuberculosis in guinea pigs. After intravenous inoculation rabbits developed tubercles in the lungs and kidneys, and in one intravenously inoculated rabbit tuberculosis of the joints and bones was found, the foci persisting as long as 256 days.

AN ATTEMPT TO TRANSMUTE THE "R" INTO THE "S" COLONY BY CULTIVATION ON MEDIA CONTAINING HOMOLOGOUS AND HETEROLOGOUS ANTISERA

We are ignorant as to the interrelationship of the "R" and "S" microorganisms. As stated before, there is sufficient experimental evidence that in cultures of pathogenic microörganisms there are mainly two types of bacterial cells, known as "R" (rough) and "S" (smooth). There are known to be other intermediate types, which we shall disregard for the present, as the biology of bacteria is very complicated and little understood. We can merely speculate as to what takes place during the dissociation.

Every "S" cell is probably continuously dissociated into "R" and "S" cells during reproduction, while the "R" cell, in all probability, reproduces mainly "R" cells, which, as their growth proceeds, eventually predominate, thus reducing the virulence of the culture, though not completely. If cultures which have apparently lost their virulence are inoculated into animals and again recovered from the animal tissues, the "S" cell may then again predominate. This may indicate that outside the body the microörganism has a tendency to dissociate into "R", while in the body it may propagate into the "S" cell.

It has been observed by many investigators that the "R" cells of pathogenic bacteria cannot be mutated into the "S" cells outside the animal body by the ordinary methods of cultivation. However, such a mutation can be accomplished in some instances by cultivating the "R" cells in media containing 5 to 10 per cent homologous antiserum, that is, serum produced by inoculating animals with "R" microörganisms. By such a method of cultivation Soule (10) has been able to transmute the "R" into the "S" in *B. subtilis* and Dawson and Avery (11) in the pneumococcus.

An attempt was made to follow this method in the cultivation of the "R" colony of *BCG*. If this "R" colony, by cultivation on its homologous antiserum, could be reversed into the "S" type, and if the cultures so

obtained were virulent for guinea pigs, then the question of spontaneous tuberculosis and accidental contamination would be conclusively settled.

The following method was used in producing antiserum:

Rabbits were sensitized with either heat-killed or living "R" microörganisms of *BCG.* In some instances the bacilli were triturated, made into a suspension, and heated at 100°C. for one-half hour. Suspensions of living microörganisms were inoculated into other animals either intraperitoneally or intravenously. After four to six weeks the rabbits were bled, and the complement-fixation and precipitin tests were made. In practically every instance complement-fixation was positive, while in only one rabbit were we able to get a definite precipitin reaction to the ring test.

First Attempt to Transmute "R" into "S" Colony: Homologous rabbit serum, obtained from animals inoculated as described above, was added to Proskauer and Beck's synthetic medium in 10 per cent proportion. The flasks were incubated for several days, to test their sterility, and were then inoculated on the surface with individual "R" colonies, subinoculations being made every two weeks. The "R" colonies did not grow very well on this medium. After eight transfers the growth had not changed its form, and appeared like the original typical "R" colonies. From this eighth transfer a small amount was removed, triturated, and inoculated subcutaneously into two guinea pigs. One died on the 23rd day and showed only localized abscesses. The contents of the localized abscesses were inoculated into two other guinea pigs. One of the second inoculated animals died in 75 days of pneumococcus pleurisy and no tuberculosis could be found, while the other is still living six months after the inoculation. The last of the first two animals died of an intercurrent disease and no tuberculosis could be found at autopsy.

Second Attempt to Transmute "R" into "S" Colony: The antiserum was prepared as follows:

Large rabbits were inoculated intravenously on two occasions five days apart with 1.2 to 4 mgm. of a suspension of an "R" colony, which had been heated at 100°C. for one-half hour. One month later a suspension of living "R" colony was inoculated into the same animals. Only a single dose of living microorganisms was given. The animals were bled ten weeks after the last inoculation, but on testing for antibodies the serum was found weak. They were again inoculated intravenously with 2.5 mgm. of living "R," and the serum again tested two weeks later. Rabbit anti-"R" and anti-"S" sera were added to Sauton's fluid medium to 10 per cent, and seeded with a typical "R" colony. Transfers were made every week. Animal inoculations were made to test the

virulence after the second, fourth, seventh and ninth transplants. Two guinea pigs were used for each experiment. At the same time that the animals were inoculated, a small amount of the growth was triturated, filtered, and plated on gentian-violet-egg medium, the object being to compare the cultural characteristics of the microörganism after cultivation of the "R" colony in anti-"R" serum with the original "R" seed.

The Influence of Anti-"R" Serum on "R" Microörganisms

Results of Animal Inoculations: Second Culture Passage: Two guinea pigs were inoculated subcutaneously with a heavy suspension of anti-"R" culture. One died on the 24th day. The lymph nodes of this animal were caseous; they were triturated, and subinoculated into another animal. The second passage animal died on the 32nd day with caseous iliac and inguinal lymph nodes and no other evidence of tuberculosis. The second animal from the first inoculation is still living after ten weeks.

Fourth Culture Passage: Subcutaneous inoculations were made into two guinea pigs. One died in 28 days of a paratyphoid infection. Tuberculosis was present at the site of inoculation, and the inguinal lymph nodes were very much enlarged. The second animal died on the 33rd day. There was tuberculosis in the omentum accompanied with peritonitis. The mesenteric, iliac and inguinal lymph nodes were very much enlarged and caseous. The spleen and liver contained many tubercles. This animal presumably died of tuberculosis.

Seventh Culture Passage: Two guinea pigs were inoculated with anti-"R" culture (0.25 mgm.). On the 52nd day one died of tuberculous pneumonia and extensive tuberculosis of the spleen and the liver. The other animal is still living 54 days after the inoculation.

Ninth Culture Passage: Two guinea pigs were inoculated with a suspension of anti-"R" culture (0.25 mgm.). One of the animals died on the 37th day, and autopsy showed extensive tuberculosis of the spleen, liver and lungs. The other animal is still living 39 days after the inoculation.

The Influence of Anti-"S" Serum on "R" Microörganisms

The "R" colony was cultivated on Sauton's medium containing 10 per cent of anti-"S" serum which was prepared as follows:

Rabbits were inoculated intravenously with two doses of 1.8 and 4 mgm. of living "S" colony five days apart. One month later a third inoculation of 4 mgm. of living "S" was given intravenously, which was again repeated after

three weeks. The animal was bled 17 days after the last inoculation. Sauton's medium, containing 10 per cent anti-"S" serum, was used as described above. Transplants were made every week, and simultaneously a small amount of the growth was suspended in saline solution and inoculated into guinea pigs. A filtered suspension was smeared on gentian-violet-egg plates at the same time. The animal inoculations were made on the dates of the second, sixth, eighth, and eleventh transplants.

Second Culture Passage: Two guinea pigs were inoculated subcutaneously with anti-"S"-serum cultures. One died on the 97th day, and the second on the 99th day, with tuberculosis of the spleen, liver and lungs. The cause of death was presumably tuberculosis.

Sixth Culture Passage: One animal was inoculated intraperitoneally and another subcutaneously. The first died on the 39th day, and showed tuberculosis of the lymph nodes, lungs and peritoneum; and the second on the 43rd day, with extensive tuberculosis of the lungs, liver and lymph nodes. In the preparation of the anti-"S" serum the rabbits were inoculated with bacilli from a living "S" colony, and some living microorganisms might have conceivably been present in the serum carried over from the blood, though this is unlikely. Control inoculations of the serum were not made.

Eighth Culture Passage: Two guinea pigs were inoculated subcutaneously and are living on the 38th day.

Cultural Studies

On gentian-violet-egg plates, which were inoculated from various culture passages, single colonies developed. The structural characteristics were studied and the type determined. In the following table the observations are recorded:

Sauton's medium

SUBCULTURE	ANTI-"R" SERA; HOMOLOGOUS	ANTI-"S" SERA; HETEROLOGOUS
First	Atypical "R" colonies	Atypical growth
Second	Atypical "R" colonies	Atypical growth
Third	Atypical "R" colonies	Atypical growth
Fourth	Atypical "R" colonies	Atypical "R" colonies
Fifth	Atypical "R" colonies; few "S" colonies	Atypical "R" colonies
Sixth	"R" and "S" colonies	Atypical "R" colonies
Seventh	"S" and "R" colonies	Atypical "R" colonies
Eighth	Mostly "S" and some "R"	"R" and "S" colonies

From the table it can be seen that when the "R" microörganisms were cultivated on Sauton's medium that contained anti-"R" serum, atypical "R" colonies developed up to the fourth subculture, after which the growth consisted of both "R" and "S" and few atypical colonies. The eighth subculture revealed a large number of "S" colonies and only a few of the "R" type. This transmutation was not so striking, from a cultural standpoint, when the microörganism was cultivated on anti-"S"-serum medium. It took many more subcultures to develop the "S" colonies. At present the effect of normal rabbits' sera on transmutation is under consideration.

DISSOCIATION OF A ONE-YEAR-OLD BCG CULTURE

An attempt was made to dissociate "R" and "S" colonies from the second glycerol-bile-potato culture sent us by Calmette, which had been kept in the refrigerator for over a year. A small amount of the growth was removed, and inoculated on glycerol-bile-potato plates. Within three weeks a growth developed. Grossly some of the colonies were very much like the "R" form. The whole mass was removed, triturated in salt solution of pH 7.8, and filtered through several layers of Whatman paper no. 5. A heavy suspension was inoculated on the surface of gentian-violet-egg plates.

In figure 1a, plate III, it will be noted that the colonies are irregular, resembling the "R" colony, while in the background is seen a thin, spreading, veil-like growth extending into the medium (plate III, 1b). A portion of this growth was removed, triturated, filtered, and inoculated on other gentian-violet-egg plates. From this veil-like growth many colonies similar to the "S" (plate III, 2c and 3, and plate IV, 2) were obtained. Animals have been inoculated with this culture, and are under observation at present.

It seems that after several careful subcultures on plates the "R" and the "S" microörganisms can be dissociated even from cultures kept in the refrigerator for a year or more.

Discussion and Summary

In the preceding studies we have presented observations made on cultures of *BCG* obtained from three different sources.

The appearance of the growth in the original cultures does not vary

from that of human or bovine bacilli. Tuberculin (O.T.) can also be prepared from the filtrates of broth cultures of *BCG*.

Animals inoculated with the microörganism become hypersensitive to tuberculin, the degree of hypersensitiveness depending on the method employed. Intraperitoneal inoculation is probably the most effective, then come intratesticular, subcutaneous, intraocular, intravenous, intracardiac and peroral.

Complement-fixing antibodies can develop in rabbits very readily, reacting not only with undissociated *BCG* antigen, but also with antigen prepared from H37 (a *moderately* virulent human strain). Precipitins are not readily formed by *BCG* inoculations. Very similar results in producing antibodies can be obtained with the dissociated "R" and "S" colonies.

Tuberculosis was present in four animals inoculated with Watson's (*BCG I*) culture when they were killed on the 84th day. Only two of the remaining four animals died presumably from generalized tuberculosis; in the other two, which were killed eight months after the inoculation, no trace of tuberculosis could be found. There is no doubt that all eight animals were infected, as indicated by the tuberculin skin test, which was positive in all. But why only two out of the whole group developed progressive disease could not be explained at that time.

Tuberculous changes were set up in healthy guinea pigs and rabbits inoculated with the two original cultures received from Dr. Calmette. In most instances the lesions once established had a tendency to heal, and in time retrogress, leaving no trace. However, in some animals considerable tissue damage was done by the microörganism. Some that died early from intercurrent disease showed tuberculosis in the lymph nodes and spleen, and sometimes in the liver and lungs. The attempt to increase the virulence of *BCG* by animal passage was successful in one instance. The bacilli obtained from intratesticular passage from animal to animal seemed to increase their virulence to such a degree that they produced progressive tuberculosis not only in guinea pigs, but also to some extent in rabbits.

We have succeeded in dissociating the *BCG* strain into two so-called "R" and "S" colonies, and have described the method in detail. The "R" colony is probably not very pathogenic, and grows with a rather smooth surface and best on fluid media with a reaction of pH 5.5–7.2 (optimum 6.4), changing the reaction of the medium from the acid to the alkaline side. The "S" colony appears to be of a different cultural

structure when compared with the "R". During the metabolism of the "S" microörganism on Sauton's medium the reaction is changed from pH 6.4 to pH 5.5. Both of these colonies can produce tuberculin in fluid media. The "R" colony can be cultivated readily on glycerol-bile-potato, while the "S" does not develop a visible growth. The "R" colony, inoculated subcutaneously into animals, has a tendency to heal, and the lesions completely disappear after two to four months. The "S" colony invariably produces progressive tuberculosis in guinea pigs and occasionally in rabbits.

Intravenous inoculation of *BCG* in rabbits and guinea pigs produces a different result as far as the progress of the disease is concerned. The "S" colony establishes progressive tuberculosis within three weeks in guinea pigs, the disease being very extensive and usually terminating in death. Even the "R" colony, when inoculated intravenously, may sometimes produce fatal tuberculosis. Why the "R" colony, which apparently is avirulent, should produce tuberculosis in guinea pigs and rabbits when this portal of entry is employed, is a mystery for which we can suggest a tentative explanation. First, there is the possibility that the "R" colony is not completely free from "S" microörganisms, and, second, mutation of "R" into "S" microörganisms may take place in the animal body. It has been pointed out elsewhere that when "R" microörganisms are cultivated on anti-"R" serum they may mutate and develop into "S" colonies. If this can be accomplished outside the body, it is reasonable to assume that the same mutation will take place within the animal body. A production of antibodies follows the inoculation of "R" colonies. Many microörganisms inoculated probably perish; however, some that survive may begin to grow in the tissues and, probably through contact with these antibodies, develop into "S" microörganisms, thus leading to progressive disease. Though we have as yet no experimental evidence to uphold this hypothesis, we feel that the explanation is not improbable. Nobel also obtained progressive tuberculosis in guinea pigs by the same method of inoculation with the undissociated *BCG* culture. We are not in a position at present to explain what biological relationship exists between the "R" and the "S" colonies if they are simultaneously present in the animal body, and this phase of the subject is now being studied in our laboratory.

Attempts have been made to transform the "R" into the "S" form by cultivating it on Sauton's medium containing anti-"R" or anti-"S" serum. In the first series of cultures we obtained no results, for the rea-

son probably, as pointed out elsewhere, that the "R" colony was cultivated on Proskauer and Beck's synthetic medium with a pH of 7.6 which is not a favorable reaction for its development. When Sauton's medium, containing the anti-"R" serum was used, transmutation took place more readily. Gentian-violet-egg plates, seeded at the time culture transfers were made, showed that the "R" colonies were gradually replaced with a growth having characteristics like those of the "S" colony. In many instances animals inoculated with these antisera cultures developed progressive disease.

We shall refrain from drawing any conclusions at present as to the significance of this transmutation for the reason that the investigation has not progressed far enough. The question naturally arises, how did this culture, which was originally a virulent bovine microörganism, come to lose its virulence? We believe that at the time of isolation the microorganism was undoubtedly virulent for small laboratory animals. The suggestion is offered in explanation that upon continued cultivation on glycerol-bile-potato medium the "R" colonies developed for the most part, while the "S" colonies probably did not grow but enough of them still remained alive and were carried along in subculturing. Further subcultures made on the same medium eliminated more and more of the "S" forms until after several hundred subcultures there were only a few of the "S" bacilli remaining, while it is very likely that at the beginning they were present in large numbers.

If the observations on the mutation of the "R" into the "S" form can be repeated, it is possible that the "R" colony, although relatively nonpathogenic at present, may be converted into the virulent "S" colony by growing it *in vivo* or *in vitro* in anti-"R" serum.

CONCLUSIONS

1. The data presented in these studies indicate that the *BCG* microorganism in undissociated form is not very virulent for guinea pigs and rabbits. Progressive tuberculosis occurs rarely, but it does occur.

2. We are still ignorant in regard to the complete life-cycle of bacteria, and among them the tubercle bacillus. The virulence of *BCG* can probably be kept at a low level by cultivating it on glycerol-bile-potato medium, but if it is to be used as a vaccine we must bear in mind that the human body is not to be compared to glycerol-bile-potato as a medium for its continued viability and development.

3. No one can predict what may happen in the course of time if *BCG* is implanted in the human body and if accidentally carried from human being to human being, or what transformations may occur after such a train of events. There are indications that the avirulent "R" microorganism may be transmuted into the more virulent "S" form by cultivation of the former on a medium containing its antiserum. At present we can only suggest the possibility that this reversed phenomenon may take place in the human body.

4. Therefore, as a result of the foregoing studies involving over 250 guinea pigs and rabbits, we believe that the use of *BCG* in prophylactic immunization may be a dangerous procedure at present. Nevertheless we are open to a change of opinion if further experiments reveal that the interpretations of the foregoing observations are erroneous.

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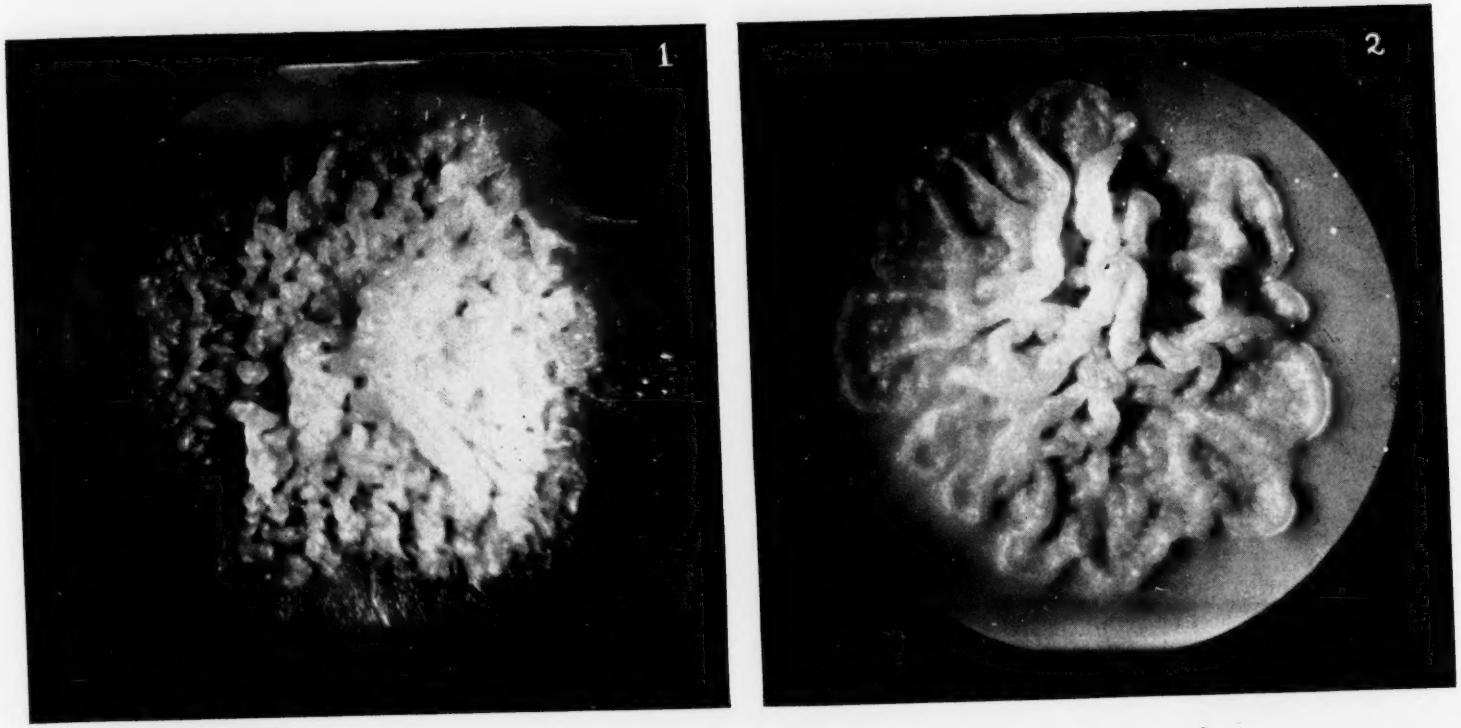
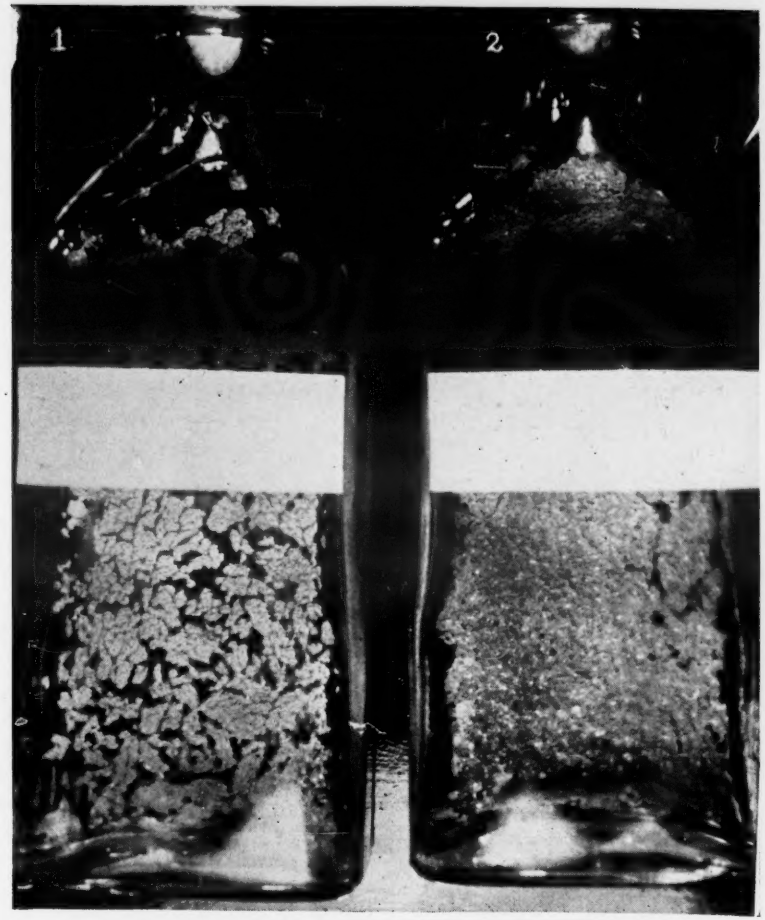
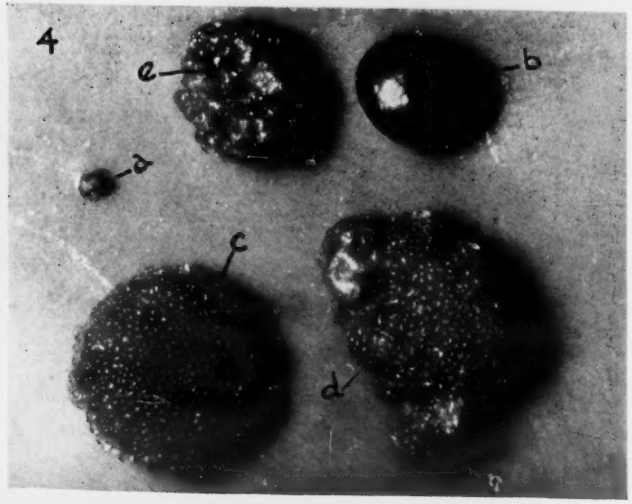


PLATE I. Microphotograph of *BCG* colonies cultivated on gentian-violet-egg medium
1: "S" colony. *2:* "R" colony. × 20.

ment. First stage *a*, second *b*, third *f*, fourth *c*, fifth *d* and sixth *e*.





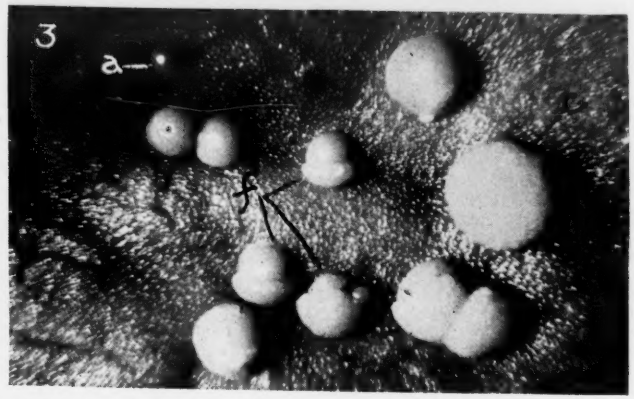
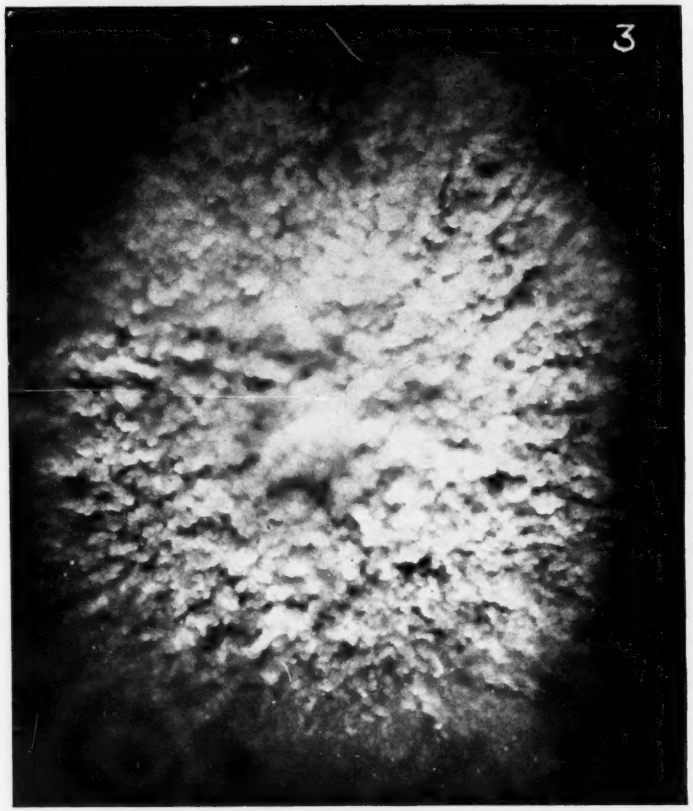


PLATE II. Microphotograph of dissociated *BCG* cultivated on Sauton's medium pH 6.4, twenty days' growth. Three-quarters natural size.
1: "R" colony. *2:* "S" colony. *3* and *4:* "R" colony cultivated on glycerol-bile-potato plates, magnified × 30, showing various stages of development. First stage *a*, second *b*, third *f*, fourth *c*, fifth *d* and sixth *e*.



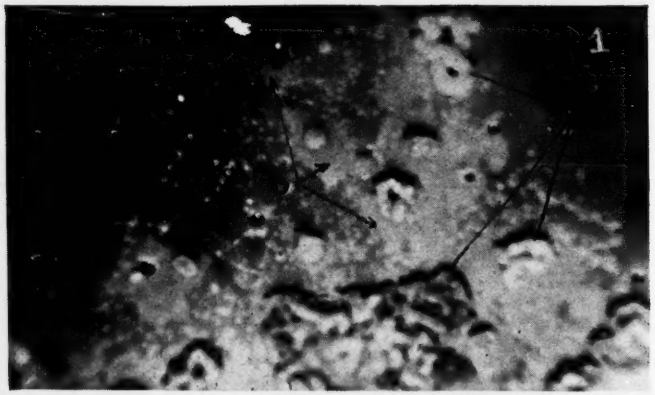


PLATE III. Figure 1 represents *BCG* colonies on gentian-violet-egg medium from culture kept in refrigerator for one year. a: "R" colonies. b: Growth of "S," which on future subculturing develops "c" in figure 2. Figure 3 is "c" magnified 40 ×.

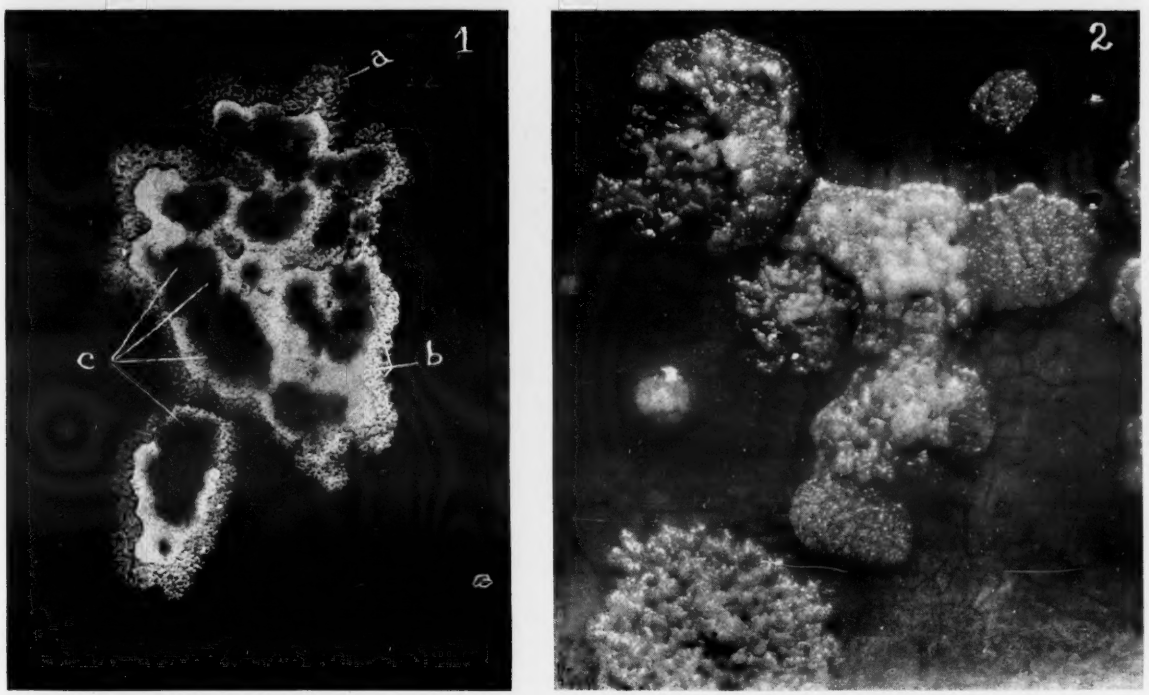


PLATE IV. Figure 1 represents 262 days' culture of "S" on gentian-violet-egg plate, natural size. At the start there were 10 to 12 colonies, which gradually increased in size until finally there was a solid mass. The periphery *a* appears to be the 'S" colony. The original colony is replaced with the "R" colony, growth *c*, and *b* is autolytic area.

Figure 2 is growth developed from colonies seen in plate III, figure 2.

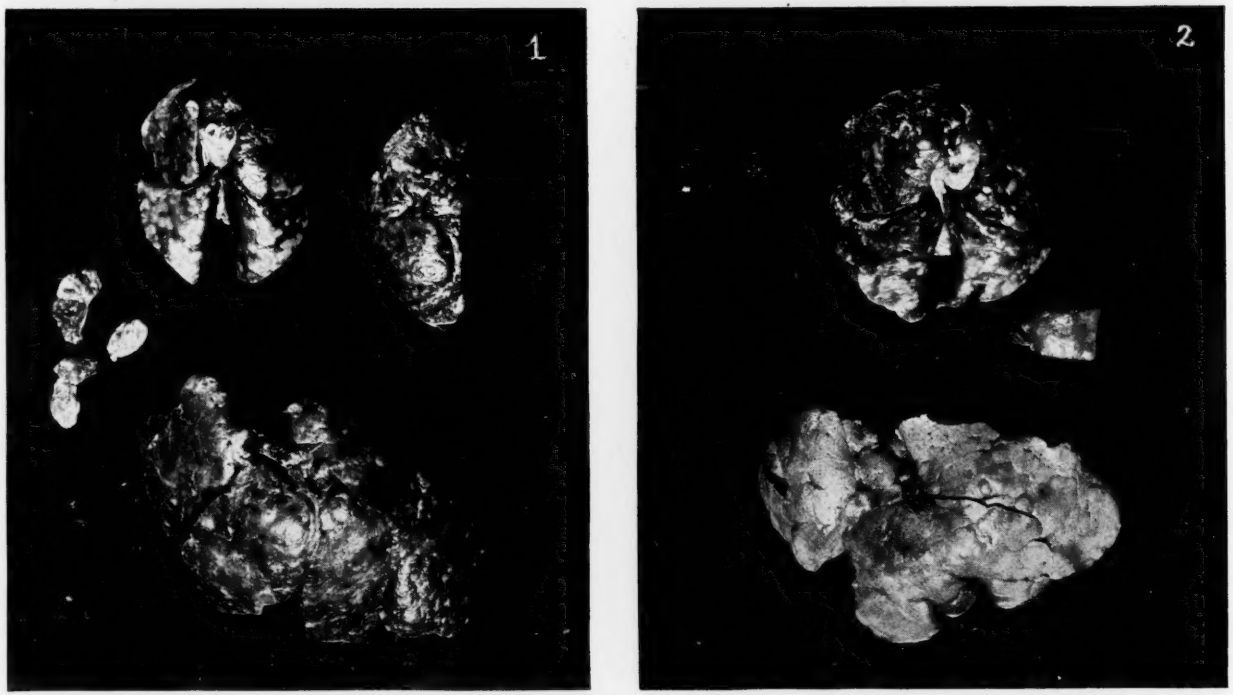


PLATE V. Figure 1: Lungs, spleen, liver and lymph nodes of guinea pig, which was inoculated with the lymph nodes of another guinea pig, which was itself inoculated with the lymph nodes of the testicular passage. This latter developed extensive tuberculosis. The original inoculation was made with undissociated *BCG* which came from the Pasteur Institute.

Figure 2: Lungs, liver and portion of the spleen of a guinea pig following intracardiac inoculation with a suspension of "R" colony. The animal died on the 375th day with tuberculosis of the lungs, liver and spleen.

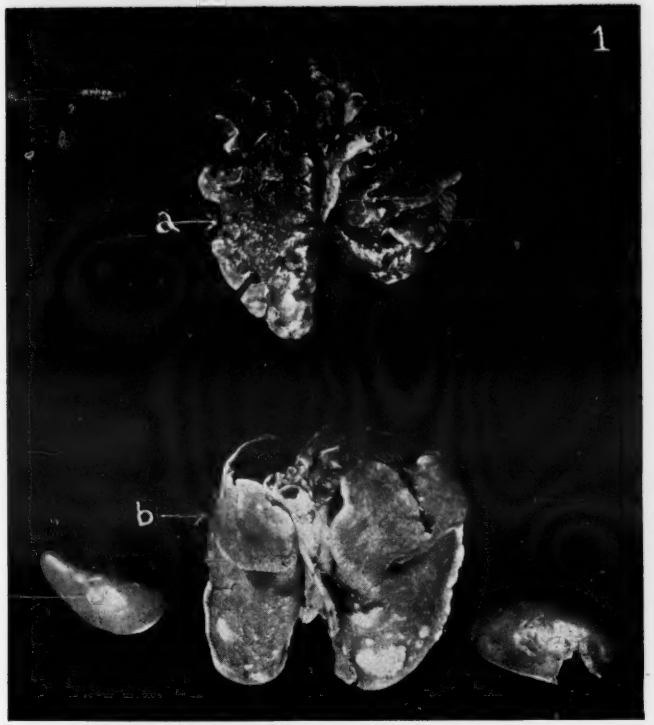


PLATE VI. Figure 1a: Lungs of rabbit inoculated intraperitoneally, first with heat-killed suspension of "R" colony. This was followed one month later with an intravenous inoculation of 5 mgm. of living "S" colony. The animal died on the 106th day with tuberculosis of the lungs and kidney.

Figure 1b: Rabbit inoculated subcutaneously with heat-killed suspension of "S" colony. This was followed with an intravenous inoculation of living "S." The animal was killed on the 66th day. Large caseous foci in the lungs; few tubercles in the kidney.

Figure 2: Lungs, liver and spleen of guinea pig. Intraocular inoculation of 0.2 mgm. of suspension of "S" colony. Animal died on the 91st day of generalized tuberculosis.

PLATE VII. Rabbit inoculated intravenously with tuberculous material from a passage guinea pig. Tuberculosis in the bones and joints.

THE ISOLATION OF THE TUBERCLE BACILLUS FROM SPUTUM

A Comparative Study of Petroff's and of Corper and Uyei's Methods

MOTI MALKANI[1]

The isolation of the tubercle bacillus from contaminated material presents many difficulties even in the hands of experienced workers. There is no method devised up to the present which does not fall short of being ideal. Probably the best method of obtaining primary cultures is by animal passage, but it requires a long time for the animal to develop tuberculosis and approximately 4 to 6 weeks to develop cultures made from the infected tissues. Therefore, this method is of limited practical value.

The introduction of the antiformin method by Uhlenhuth (1) for digesting the sputum and concentrating the tubercle bacilli paved the way for Brown and Smith (2) and R. C. Paterson (3) to utilize it in isolating the tubercle bacillus from contaminated materials. A few years later successful isolations reported by these authors were corrob orated by Griffith (4), who, in turn, slightly modified the original method.

In 1915 Petroff (5) reported a new method, utilizing for digestion sodium hydroxide which could be easily neutralized with hydrochloric acid. He used an egg medium to which gentian-violet dye was added to eliminate the gram-positive microörganisms, following an observation made by Churchman. At the time Petroff reported 95 per cent of positive isolations by his method, Mitchell and Simmons (6) 80 per cent, Keilty (7) 66 per cent, Stewart (8) 64 per cent, and Corper, Fiala and Kallen (9) 27.3 per cent. The discrepancies can probably be accounted for by the varied techniques employed, as we shall point out later.

A number of modifications have been offered since the appearance of the original method, but none has proved of enough value to lead to its wide adoption. In 1925 Loewenstein (10) suggested the use of sulphuric acid in place of sodium hydroxide for digesting contaminated

[1] Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

materials, and in his hands it has proved to be more suitable. More recently, Corper and Uyei (11) reported a comparative study of Petroff's method with the one devised by them, which, in essentials, is the same as Loewenstein's acid-digestion but substitutes potato-crystal-violet for the gentian-violet-egg medium. These authors concluded that the method and medium devised by them were superior to those of Petroff. It seems that if the method advocated by them can eliminate contaminating microörganisms more efficiently than Petroff's method, without impairing the growth of the tubercle bacillus, it should be of great value for the reason that every method can stand a great deal of improvement.

A survey of the problems brings out three main factors, which, as can be pointed out, are responsible for successful results, namely, the freshness of the material, the method of digestion and neutralization, and, finally, the medium.

By digesting the sputum with either sodium hydroxide or sulphuric acid many of the microörganisms are destroyed, and the dye, having a bacteriostatic property, will prevent the development of many other secondary microörganisms which have escaped destruction. Even then, some do occasionally develop. Contaminations, occurring in culture tubes which have been seeded with the digested sediment, may have had their origin either in the original material or from the air. No matter how careful one may be, this latter method of contamination does occur occasionally.

The primary object of the studies about to be reported was to correlate Petroff's medium and method with that advocated by Corper and Uyei.

BACTERICIDAL AND BACTERIOSTATIC STUDIES

An attempt was made to find out what dye or combination of dyes, with or without sodium ricinoleate, has an effect in inhibiting the growth of the most common contaminators found in cultures. From previous experiments it seems that molds, *B. prodigiosus* and the staphylococcus are the predominating contaminators, which consequently were used in this study.

A one per cent alcoholic solution of thymol was added to egg medium in the proportions of 1–1,000, 1–2,000, 1–5,000, 1–10,000, 1–20,000 and 1–40,000. After the addition of this substance the medium was inspissated by the usual method, and the microörganisms mentioned above were cultivated on it. It was found that thymol in the dilutions used exerted no inhibitory action on the microörganisms mentioned.

As pointed out by Churchman, gentian-violet inhibits a large number of the gram-positive microörganisms, while on the other hand some of the gram-negative microörganisms can be inhibited by basic fuchsin. It seemed possible on this account that a combination of these two dyes added to the egg medium might exhibit better bacteriostatic properties, but egg medium containing these two dyes in combination and in various dilutions did not prevent the development of the microörganisms studied.

In another set of experiments sodium ricinoleate in various proportions was added with or without the above dyes. Numerous combinations were made, but not a single one proved to be of any value. Sodium ricinoleate, when incorporated in a medium containing these two dyes, did not inhibit the growth of human and avian tubercle bacilli and a nonpathogenic acid-fast microörganism, provided the concentration was not more than 1–1,000.

The bacteriostatic properties of brilliant- and malachite-green were also studied. Egg media, containing the dyes separately in proportions of 1–10,000 to 1–100,000, did not prevent the growth of contaminating microörganisms. Laboratory strains of tubercle bacilli gave a good growth, and in one instance tubercle bacilli from sputum were successfully cultivated on the above concentration.

ISOLATION OF THE TUBERCLE BACILLUS FROM THE SPUTUM

Three groups of studies were made. The first series consisted of gentian-violet-egg medium made up in petri dishes, a method recently advocated by Petroff for obtaining single colonies. In the second and third series the medium was made up in tubes. Several factors were taken into consideration in the study.

Experiment 1

Egg medium, containing the gentian-violet dye, was made up in dilutions of 1–20,000 and prepared by the usual method. After inspissation the plates were left in the incubator for three days, to test their sterility. Immediately after taking the plates from the incubator and while still warm, special rubber bands were put around them and they were then left at room temperature. This method of sealing the plates, recently described by Petroff (12), prevents contamination and dehydration to a large extent.

The sputum was collected in sterile wide-mouthed bottles and each specimen divided into two equal portions. To one of the bottles an equal part of sodium hydroxide was added and to the other sulphuric acid, 6 per cent

by volume, (sp. gr. 1.84; content about 98 per cent). They were well shaken and incubated for one hour. At the end of this time the mixtures were centrifugated. The sediment of the acid digestion was not neutralized, but to the alkaline sediment one drop of phenol-red was added and then neutralized with normal hydrochloric acid. Both sediments were then inoculated on the surface of petri dishes containing gentian-violet-egg (1–20,000) medium. The surface was well streaked, and rubber bands were put over the petri dishes to prevent dehydration and contamination. They were incubated as usual and observed weekly.

Twenty specimens of sputum, and one plate for each digestion were used. At the end of the seventh week the primary isolation of the tubercle bacillus in this experiment could be summarized as follows:

Appearance of Growth: When both digestions were considered together, 19 specimens gave positive results, or 95 per cent. The sodium-hydroxide digestion gave growth with 15 specimens, or 75 per cent, while the sulphuric-acid digestion gave a growth in 16, or 80 per cent. The sodium hydroxide gave growth in three cases in which there was no growth by the acid digestion for the same sputum. On the other hand, acid digestion gave growth in four cases not giving any growth by the alkaline digestion. In this series there was massive contamination in two plates of the sodium-hydroxide digestion, preventing the growth of tubercle bacilli. In plates inoculated with the acid-digested sputum there was no such contamination. The reason for the contaminations in the alkaline digestion will be pointed out later in this study.

Experiment 2

In the second series we used three different media, one tube each of (1) plain glycerol-egg, (2) glycerol-egg-gentian-violet (1–20,000), and (3) Corper's (11) medium, for each method of digestion. Twenty-nine sputa were collected in sterile wide-mouthed bottles, and digestion, in the majority of the cases, was carried out in sterile test-tubes as recommended by Corper. The tubes containing the acid (H_2SO_4 6 per cent (*wt.*)) and the alkaline-digested (N/1 NaOH) sputa were incubated, the former for one-half hour and the latter for one hour, transferred to sterile test-tubes, centrifugated, and the supernatant fluid discarded. The sediment of the acid digestion was not neutralized, but to the sediment of the alkaline digestion one drop of phenol-red was added and neutralized as before. They were inoculated into three media. The total number of culture tubes used in this experiment was 174. At the end of eight weeks the results may be summarized as follows:

Taking into consideration, first, the methods of digestion, that is, alkaline and acid together, positive results were obtained in 27 out of 29 sputa, or a percentage of 93.1 of all three media. With only sodium-hydroxide digestion the three media gave a growth in 25 cases, or 86.2 per cent, and with only acid

digestion a growth in 23 cases, or 79.3 per cent. Considering the medium, gentian-violet-egg and Corper's medium only, a uniform growth appeared in 15 cases, or 51.7 per cent. Using the alkaline method of digestion and gentian violet-egg medium, a growth appeared in four cases, or 13.8 per cent, which gave no corresponding growth using the acid digestion and Corper's medium. When Corper's method and medium were used, a growth appeared in 7 cases, or 24.1 per cent, and this growth was not present from the alkaline digestion on gentian-violet-egg medium. When both methods of digestion were used and only gentian-violet-egg medium, growth appeared in 20 cases, or 69 per cent, while isolation with Corper's medium gave growth in 23 cases, or 79.3 per cent. If we separate the two methods, sodium-hydroxide digestion on plain glycerol-egg gave growth in 69 per cent, on gentian-violet-egg medium in 65.5 per cent, and on Corper's medium in 65.5 per cent. Acid digestion gave growth on plain egg in 65.5 per cent, on gentian-violet-egg medium in 44.8 per cent, and on Corper's medium in 75.9 per cent.

Speed of Growth: As to the rapidity of growth by the two methods, it seems that it appeared in isolations made by Corper's method earlier than by the gentian-violet method and medium. Massive contaminations in this series were very much the same as those in the preceding series. By the sodium-hydroxide digestion on all media there were 12 contaminations, or 13.8 per cent, while by the acid digestion there were two contaminations, or 2.3 per cent. This high percentage of contamination by the sodium-hydroxide digestion could not be explained, and a survey of the various steps was made. It was concluded that in the sodium-hydroxide digestion the method was subjected to more manipulations, various steps being necessary in the preparation of the material for inoculation, allowing more chance for contaminations.

Experiment 3

The third series was carried on in an endeavor to check up the sources of contamination as well. A departure was made in this series from the preceding two, using Petroff's modification (12), which eliminated the steps of neutralization. Gentian-violet-egg medium was used the same as in the preceding series, that is, 1–20,000. In this series the period of digestion was the same for both reagents, namely, one-half hour, and carried on in sterile wide-mouthed bottles. The digested sputa were then put in sterile test-tubes and centrifugated. The acid-digested sediment was not neutralized, but to the sediment of the alkaline digestion a few drops of normal hydrochloric acid were added until it became opaque. It was inoculated into three test-tubes of gentian-violet-egg medium, three tubes of Corper's medium, and one tube of plain egg medium. A total number of 616 tubes were used and 44 specimens were studied. At the end of seven or eight weeks the results may be summarized as follows:

Positive growth by both methods of digestion, considering all three media together, was obtained in 40 out of 44 cases, a total of 91 per cent. When sodium-hydroxide digestion was used, using the three media, 39 specimens gave growth, or 88.6 per cent. By the acid digestion on all three media, 34 gave growth, or 77.2 per cent. Considering the medium used, there were 33 growths, or 75.0 per cent, on gentian-violet-egg by both digestions. On the other hand, using both methods of digestion but Corper's medium, there was a growth in 38 cases, or 86.3 per cent. There was agreement of growth in the two methods and media (Petroff's and Corper's) in 25 cases, or 56.8 per cent. There was growth by Petroff's method and medium and not by Corper's method, for the same sputum, in seven cases, or 15.9 per cent, while in six cases, or 13.6 per cent, Corper's method and medium revealed positive growths that were missed by Petroff's method and medium. In a very small percentage (about 2.3 per cent) plain egg medium gave growth with sodium-hydroxide digestion, and there was the same percentage of growth, that is, 2.3 per cent, in Corper's medium with sodium-hydroxide digestion that were missed by Corper's and Petroff's media, as per their methods of digestion.

In summarizing the two methods and media, sodium-hydroxide digestion gave growth on plain egg in 27, or 61.4 per cent, on gentian-violet-egg in 32, or 72.7 per cent, and on Corper's medium in 33, or 75 per cent. The acid digestion on plain egg medium gave growth in 20 cases, or 45.5 per cent, gentian-violet-egg in 25 cases, or 56.8 per cent, and Corper's medium in 31, or 70.5 per cent.

When we consider the rapidity of the growth in this series, we also find that Corper's method of digestion, using his medium, is slightly more rapid than Petroff s method and medium. In regard to massive contamination in the 616 tubes employed, 11, or 3.6 per cent, were contaminated by the alkaline digestion and 10, or 3.2 per cent, by the acid digestion, but this included all the media. If we analyze the different media we find that by the sodium-hydroxide digestion on plain egg there were five out of 44 tubes contaminated, giving 11.4 per cent, four out of 132 tubes on gentian-violet-egg medium, or 3 per cent, and two out of 132 tubes on Corper's medium, or 1.5 per cent. When acid digestion was used, four out of 44, or 9.1 per cent, were contaminated on plain egg, two out of 132, or 1.5 per cent, on Petroff's medium, and four out of 132, or 3 per cent, on Corper's medium. This low percentage of contamination in the third series explains fairly well that the steps taken in accurately neutralizing the alkaline-digested sputa allow more contaminations, and by eliminating these steps and using the modified technique, as recommended by Petroff (13), thus ensuring a stricter bacteriological technique, the development of many air-borne contaminating microörganisms can be prevented.

DISCUSSION AND SUMMARY

Brilliant-green, malachite-green, gentian-violet with basic fuchsin, with or without sodium ricinoleate, or thymol in various concentrations, incorporated in the glycerol-egg medium, do not inhibit the growth of some of the contaminating microörganisms (when planted in pure cultures) commonly present during the isolation and cultivation of the tubercle bacillus.

In a comparative study made to determine the value of a method of digestion, cultures of tubercle bacilli which have been under cultivation should not be used. Very often such cultures do reveal a growth, whereas if isolation from the sputum is attempted results may be entirely negative. We recommend therefore that in such studies a series of sputa positive for tubercle bacilli be used, in order to give us much more reliable data. A positive sputum may give a growth on one occasion and at other times may not. We cannot offer any explanation for this fact at this time.

The time of digestion of the sputum either with alkali or with acid need not be longer than one-half hour. Prolonged digestion is of no advantage in preventing contamination, and digestion longer than one-half hour may retard the development of the tubercle bacillus. We believe that contaminations may also come from the air during manipulation.

A sediment of sputum digested with sodium hydroxide can be approximately neutralized by adding a few drops of normal hydrochloric acid. Accurate neutralization does not yield a higher percentage of growths. Hence, an indicator is not necessary. Such a procedure may decrease the incidence of contamination, but a strict bacteriological technique is essential.

It is evident from the studies presented that acid digestion may prevent the growth of tubercle bacilli from a sputum, while this same sputum may give a growth by alkaline digestion. The same thing may happen with other sputa, growth appearing conversely by the acid and not by the alkaline digestion. Perhaps this variation can be explained in the light of recent studies on the dissociation of the tubercle bacillus. Recently Petroff and Branch (14) have pointed out that the "S" colony of the tubercle bacillus grows more profusely on fluid alkaline media and less so on acid media. On the other hand, the "R" colony will develop much more rapidly on acid than on alkaline media. We have also found that

in several instances in the experiment done on plates, the gross appearances of the colony-formation by the two methods of digestion do not correspond. Can it be that the "S" colony present in a sputum can be isolated better by alkaline digestion, and the "R" colony better by the acid digestion? This is only a suggestion and a further study may throw some light on this problem.

Such being the case, it seems that in order to get a constantly high percentage of primary isolations of tubercle bacilli from sputum, both methods of digestion and more than one medium should be employed.

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THE TESTICULAR ALLERGIC RESPONSE (SPERMATOCYTE REACTION) IN GUINEA PIGS FOR THE DIAGNOSIS OF TUBERCULOUS FLUIDS[1]

J. J. WIENER, JOHN E. BLAIR AND HENRY L. JAFFE

Hospital laboratories are constantly confronted with the problem of diagnosis of tuberculosis in the case of fluids suspected of coming from tuberculous foci. The routine method of guinea-pig inoculation now in use has many shortcomings. No guinea pig so inoculated should be declared nontuberculous before three or four months, since it is the experience of laboratories, where a great number of such inoculations are made, that occasionally a guinea pig, showing no general or local tuberculosis six to eight weeks after the inoculation, will subsequently develop generalized tuberculosis. The development of tuberculosis in the guinea pig is also dependent upon the introduction of a sufficient number of tubercle bacilli, and it has been shown that the introduction of fewer than ten virulent bacilli frequently fails to produce tuberculosis in the animal. Another factor is the virulence of the microörganism, which, if attenuated, may not produce generalized tuberculosis. It has been our own experience that in rare instances fluids and tissue from cases of tuberculous synovitis, showing anatomically very sclerotic tubercles in the synovial membrane, when inoculated into guinea pigs fail to give rise to tuberculosis. Aside from these objections, the diagnosis of tuberculosis in the spleen and liver of animals known to be inoculated with material from tuberculous foci is sometimes extremely difficult to the pathologist, since the anatomical features of the tubercle are frequently quite different from those seen in human tuberculosis; the diagnosis then rests on the finding of tubercle bacilli in the tissues, which of itself is often very difficult. Last, but not least, is the possibility of misinterpreting nontuberculous lesions in the spleen or liver of guinea pigs; this error may very frequently arise when histological examinations are not made of these tissues, and may even occur, but less often, when the lesions are examined microscopically.

[1] From the Laboratory Division, Hospital for Joint Diseases, New York City.

It is therefore seen that the use of some other method, either to supplement or replace the present method of guinea-pig inoculation, would be of decided value. A suggestion for experimental work along this line was found in the recently reported work of Long (1), who, in studying the reinfection of guinea pigs through the testis, found that this organ was highly sensitive to the inoculation of tubercle bacilli or tuberculin in animals previously infected with tuberculosis. The response in the testis was typical of all specific allergic reactions in animal tissues sensitized to tuberculin by the presence of a tuberculous focus in the body. Hyperaemia, oedema, necrosis and cellular infiltration constitute the different stages of the reaction. The necrosis is most marked in the spermatocytes and spermatogonia, and Long applied the term of "spermatocyte reaction" to this phenomenon (2).

It occurred to us that in cases of fluids suspected of having a tuberculous aetiology this reaction might prove to be of diagnostic value, since these fluids must have a considerable concentration of tuberculin or tuberculin-like material. As a preliminary experiment, Long's work on the spermatocyte reaction with tuberculin was confirmed (3).

After confirmation of this work, we proceeded to our experimental work with body fluids. The fluids tested were obtained from pleural, joint, and abdominal cavities, and pus from abscesses. They were examined by the following technique:

1: Direct smears of all fluids were examined for tubercle bacilli and other microörganisms, and cultures were made on dextrose hormone media.

2: The routine method of diagnosis was employed, by injecting about 3 cc. of the fluid subcutaneously into a guinea pig; this animal was autopsied after six to thirteen weeks, and examined for tuberculosis.

3: For the spermatocyte reaction, mature male guinea pigs, weighing at least 400 to 500 gm., were used, these animals having been inoculated four weeks previously in the axilla with a virulent strain of tubercle bacilli. Into the centre of the right testis of a tuberculous guinea pig from 0.1 to 0.3 cc. of the suspected fluid was injected, and an equal amount was similarly injected into the right testis of a nontuberculous animal, to serve as a control. Five to seven days after the testicular inoculations, the tuberculous and nontuberculous guinea pigs were killed. The testes were fixed either in 10 per cent neutral formalin or in Zenker-formol solution, after first nicking the capsule at one point with scissors to ensure good fixation. Three sections were cut at right angles to the long axis of the testes from representative portions, and the sections were embedded in paraffine and stained with haematoxylin and eosin. By the above procedure we had a triple control for every fluid.

In attempting this work it was our hope that fluids from tuberculous sources would give a response in the testis similar to that observed in the acute stage by Long in his work with tuberculin. The acute reac-

tion is the only reaction which would be of value, as we were trying to develop a method which would reduce the time necessary for diagnosis. The acute reaction which follows the injection of tuberculin into the testis of a tuberculous guinea pig consists principally of a marked degeneration of the cells of the tubules, and infiltration of cells between the tubules. Long believed that this was a specific allergic response. The tuberculous fluids from the various sources which we tested nearly always gave a reaction similar to that obtained with tuberculin. However, a fluid from a case of tuberculous meningitis failed to elicit such a response, and some fluids from nontuberculous sources caused degeneration of the tubules, the latter casting a doubt upon the specificity of the reaction. A total of thirty-five fluids was studied.

Tuberculous Fluids: Twelve fluids were proved by direct smear or guinea-pig inoculation to be tuberculous. Of these twelve, eleven gave a positive spermatocyte reaction with degeneration, usually involving practically all the tubules; in no instance was there less than 60–70 per cent of destruction, and in the majority of cases 80–100 per cent of the tubules were involved. Such a positive reaction is seen in figure 1 (control, figure 2). One tuberculous spinal fluid produced no degeneration when injected into the testis of a tuberculous guinea pig. On direct examination we could find no tubercle bacilli in this fluid. Three cubic centimetres of the fluid were injected into a control guinea pig for diagnosis by the usual method. The guinea pig was killed at the end of eleven weeks; it was in good condition, with no demonstrable tuberculosis. On histological examination a few sclerotic lesions were found in the spleen, which, while not unequivocal, were probably tubercles. In the discussion we will consider this discrepancy in the response. Nearly all the tuberculous fluids, when inoculated into the testes of nontuberculous guinea pigs in amounts equal to that similarly injected into the tuberculous animals, produced no reaction whatsoever. Two of the fluids caused from 3 to 10 per cent of degeneration, which was localized, in contrast to the generalized destruction which these fluids produced in the tuberculous guinea pigs.

Fluids of Nontuberculous and Non-Neoplastic Origin: Fifteen fluids were known to come from cases in which there was no malignant tumor, and were shown by smear and guinea-pig inoculation to be nontuberculous. One of these fluids, from a case of chronic infectious arthritis, produced degeneration in the testis of a tuberculous guinea pig entirely similar to that caused by a tuberculous fluid. Another fluid, taken from

the pleural cavity at autopsy in a case of hypertension and cardiac failure, gave rise to a typical "spermatocyte reaction," with marked degeneration of the tubules. A third fluid, consisting of pus aspirated by the bronchoscope from a lung abscess, likewise caused marked degeneration. Two of these fluids, producing a considerable amount of destruction in the testes of tuberculous guinea pigs, caused no reaction when inoculated in similar amounts into the testes of nontuberculous animals. One fluid gave rise to a small localized area of degeneration, which was demonstrable in one of the three histological sections, and gave no reaction in the testis of a nontuberculous guinea pig. This will again be referred to in our discussion. The other twelve fluids caused no degeneration of the testes of tuberculous or nontuberculous guinea pigs (figure 3). One of these fluids, which was negative upon being tested when fresh from the body, was kept at 37°C. for nine days and injected into a second series of guinea pigs. In the testis of the tuberculous

FIG. 1. Tuberculous knee fluid in tuberculous guinea pig; 0.2 cc. of fluid injected; 5 days after inoculation. Considerable degeneration has occurred, practically no normal tubules being found. Little infiltration has taken place in this case.

FIG. 2. The left uninoculated testis of the same animal as used in fig. 1. A normal testis, in contrast to the destruction seen in the right testis.

FIG. 3. Tuberculous knee fluid in nontuberculous guinea pig; 0.2 cc. of fluid injected; 5 days after inoculation. The same fluid which caused destruction of the testis in a tuberculous guinea pig (fig. 1), has no effect upon the testis of a normal, unsensitized animal.

animal there was found a moderate degenerative reaction, accompanied by marked interstitial infiltration that was quite comparable to a "spermatocyte reaction." This would seem to be due to a toxic effect of the fluid which was not present when the fluid was fresh, and was not due to bacterial contamination, but developed upon standing. The inoculated testis of the nontuberculous guinea pig was unaffected.

Fluids from Cases of Malignant Tumor: Eight fluids, known to come from cases of malignant tumor, were examined. All were proved by guinea pig inoculation to be nontuberculous. Five of the eight produced a reaction entirely indistinguishable from a "positive" spermatocyte reaction in the testes of tuberculous guinea pigs (figure 4; control, figure 5). In contrast to the usual 80–100 per cent destruction of tubules produced by a tuberculous fluid, degeneration caused by fluids from cases of malignant tumor as a rule involved fewer tubules, and on an average about 25–30 per cent. The areas of degeneration were usually patchy

FIGS. 1–3

and localized, as distinguished from the reaction due to a tuberculous fluid, which involved the entire testis. However, these differences apparently have little significance, and are not sufficiently marked to be of practical diagnostic value. The reaction produced in these cases was due to a toxic action of the fluid, as was shown by the fact that the same fluids in the testis of nontuberculous guinea pigs usually caused from 3 to 10 per cent degeneration of the tubules.

Two of the five fluids of malignant-tumor origin giving a degenerative reaction were ascitic fluids; the other three were pleural fluids, one coming from a case which at autopsy showed carcinoma of the lung and healed apical tuberculosis. This latter fluid caused a 70 per cent degeneration of the testis of a tuberculous guinea pig and 3 per cent degeneration in the nontuberculous control. The diagnostic guinea pig with this fluid died at the end of six weeks with extensive pneumonia and suppurative pleurisy; microscopical sections showed no tuberculosis.

To summarize the above results: Of 12 tuberculous fluids, eleven (91.6 per cent) produced degeneration in the testis of tuberculous guinea pigs similar to the reaction obtained by Long, and confirmed by us, upon the injection of dilutions of Old Tuberculin into the testis of tuberculous guinea pigs (spermatocyte reaction). Of 15 fluids from cases of nontuberculous and non-neoplastic origin, three (20 per cent) gave rise to a typical spermatocyte reaction in the testes of tuberculous guinea pigs. Of 8 fluids from cases of malignant tumor, five (62.5 per cent) caused a degenerative reaction in the testis of tuberculous guinea pigs indistinguishable histologically from the spermatocyte reaction caused by tuberculous fluids. Of 23 nontuberculous fluids, then, from various sources, including synovitis, arthritis, pleural and abdominal tumors, etc., 8 (34.7 per cent) gave reactions which could easily be taken for a "positive spermatocyte reaction."

Further Experiments: Still believing that the method had usefulness, and in spite of the fact that the carcinomatous fluids and fluids known to come from nontuberculous and noncarcinomatous foci frequently gave a marked degeneration simulating a spermatocyte reaction, we began to investigate the conditions under which such fluids may produce a toxic effect entirely similar to the specific allergic reaction.

In short, as above described, we found that if a fluid, which had given a negative reaction when injected immediately after aspiration, was kept outside of the body at 37°C. for several days, it developed the ability of giving a positive reaction.

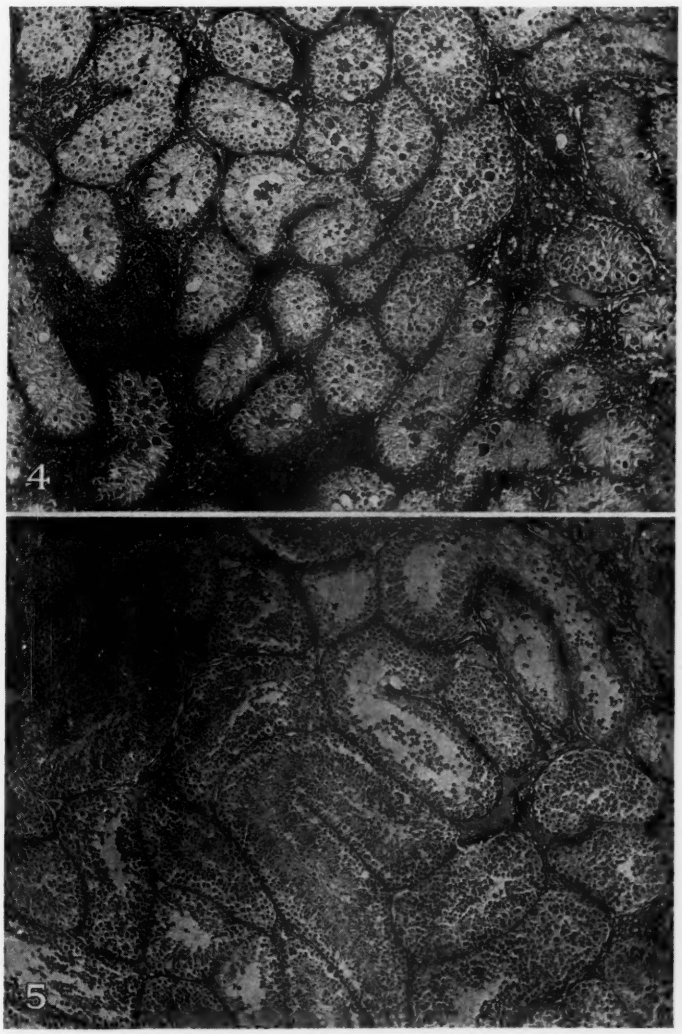

FIG. 4. Abdominal carcinoma fluid in tuberculous guinea pig; 0.1 cc. of fluid; 5 days after inoculation. Marked degeneration has occurred, together with infiltration between the tubules, giving a picture quite similar to that obtained with a tuberculous fluid.

FIG. 5. Abdominal carcinoma fluid in nontuberculous guinea pig; 0.1 cc. fluid; 5 days after inoculation. Control to fig. 4. Even in the normal guinea pig a slight amount of destruction has been produced. This is apparently due to some inherent toxicity of this type of fluid.

TABLE 1

Fluids of proved tuberculous origin

PATIENT	DIAGNOSIS	FLUID			TEST			REACTION	
		Source	Guinea pig inoculation	Smear for tubercle bacilli	Guinea pig number	Amount of fluid injected	Days	Right testis	Left testis
						cc			
F. D.	Tuberculous synovitis	Knee	+	−	72(Tb+)	0.2	5	Positive (80 per cent degeneration)	Negative
					42(Tb−)R	0.2	5	Negative	[Negative]
S. C.	Synovitis	Knee	+	−	459(Tb+)	0.1	3	Positive (80 per cent degeneration)	Negative
					5c(Tb−)	0.1	3	Negative	Negative
D. G.	Synovitis	Knee	+	−	123(Tb+)	0.1	6	Positive	Negative
					104(Tb−)	0.1	6	Negative	Negative
Y. G.	Pulmonary tuberculosis; pleural effusion	Pleural cavity	Not done (sputum +)	−	41(Tb+)	0.3	7	Positive (65 per cent degeneration)	Negative
					81(Tb−)	0.3	7	Negative (10 per cent degeneration)	Negative
A. S.	Pleural effusion	Pleural cavity	+	−	92(Tb+)	0.2	7	Positive (80 per cent degeneration)	Negative (10 per cent degeneration)
					116(Tb−)	0.2	7	Negative	Negative (1 to 2 per cent degeneration)
C. R.	Tuberculosis of tarsus	Ankle	Not done	+	70(Tb+)	0.2	5	Positive (95 to 100 per cent degeneration)	Negative
					42(Tb−)L	0.2	5	[Negative]	Negative

C. M.	Tuberculosis of hip	Subtrochanteric bursa	+	−	201(Tb+)R	0.03	6	Moderately positive	
					L	0.015	6		Slightly positive (less than right)
					148(Tb−)R	0.03	6	Negative	[Toxic action, due to another fluid.—E. D.]
M. V.	Tuberculosis of rib	Pus from abscess	+	−	165(Tb+)	0.05	5	Positive (100 per cent degeneration)	Negative (30 per cent degeneration)
					197(Tb−)L	0.05	3*	[Negative]	Negative
F. P.	Tuberculosis of wrist	Pus from abscess	+	−	192(Tb+)	0.025	5	Positive	Negative
					155(Tb−)	0.025	7	Negative (one small localized area of necrosis)	[Marked degeneration, due to inoculation with fluid from a lung abscess]
Hu.	Pulmonary tuberculosis; tuberculous meningitis	Spinal fluid	+	−	164(Tb+)	0.1	5	Negative	Negative
					197(Tb−)R	0.1	3*	Negative	[Negative]
E. D.	Pulmonary tuberculosis; infiltration of right lung	Pus from abscess	Not done	+	202(Tb+)	0.2	6	Positive (extensive necrosis with tubercles)	Negative
					148(Tb−)L	0.2	6	[Negative]	Moderate degeneration, toxic effect
S. E.	Tuberculosis of hip	Pus from abscess	Not done	+	204(Tb+)R	0.1	5	Positive (extensive necrosis)	
					L	0.05	5		Positive (less than right)
					230(Tb−)L	0.1	5	Severe degenerative changes, sufficient for "positive" diagnosis	[Negative]

* Died of pneumonia.

TABLE 2

Fluids of nontuberculous and non-neoplastic origin

PATIENT	DIAGNOSIS	FLUID			TEST			REACTION	
		Source	Guinea pig inoculation	Smear for tubercle bacilli	Guinea pig number	Amount of fluid injected	Days	Right testis	Left testis
						cc.			
T. M.	Arthritis	Shoulder	−	−	156(Tb+)	0.1	6	Negative	Negative
					189(Tb−)L	0.1	6	[Negative]	Negative
J. C.	Chronic synovitis	Knee	−	−	428(Tb+)	0.3	5	Negative	Negative
					44(Tb−)	0.3	5	Negative	Negative
C. D.	Osteoarthritis	Knee	−	−	119(Tb+)	0.1	6	Negative	Negative
					189(Tb−)R	0.1	6	Negative	[Negative]
H. H.	Chronic infectious arthritis	Knee	−	−	194(Tb+)R	0.2	5	Positive (little interstitial reaction)	
					L	0.05	5		Mild degenerative changes
					242(Tb−)R	0.2	5	Small area of degeneration in one section; two sections normal	[Negative]
R. M.	Chronic arthritis	Knee	−	−	13(Tb+)	0.05	7	Negative	Negative
					14(Tb−)	0.05	7	Negative	Negative

B. D.	Synovitis	Knee	−	−	203(Tb+)R	0.1	5	Negative	
					L	0.05	5		Negative
					228(Tb−)R	0.1	5	Negative (8 per cent degeneration in one section)	Negative
B. D.	Same fluid as above; kept at 37°C. for 9 days; sterile				200(Tb+)R	0.2	6	Marked interstitial reaction, and moderately severe degeneration	
					L	0.01	6		Less interstitial, greater tubular reaction
					147(Tb−)R	0.2	6	Negative	[Negative]
J. T.	Acute synovitis	Knee	−	−	481(Tb+)	0.1	1	Negative	Negative
					386(Tb−)	0.1	1	Negative	Negative
De.	Ascites	Abdominal cavity	−	−	207(Tb+)	0.1	5	Negative [5 per cent degeneration in one of 3 sections].	Negative
					232(Tb−)	0.1	5	Negative	Negative
Gu.	Ascites	Abdominal cavity	−	−	159(Tb+)	0.1	5	Negative	Negative
					183(Tb−)R	0.1	5	Negative	[Negative]
L. H.	Chronic cardiovascular disease	Abdominal cavity	−	−	106(Tb+)	0.1	5	Negative	Negative
					154(Tb−)	0.1	5	[Negative]	Negative
Sw.*	Syphilis	Spinal	−	−	205(Tb+)	0.1	5	Negative	Negative (testes immature)
					230(Tb−)L	0.1	5	[Degeneration due to another fluid.—S. E.]	Negative
C. B.	Acute and subacute inflammation	Pus from thigh	−	−	161(Tb+)	0.1	5	Negative	Negative
					183(Tb−)L	0.1	5	[Negative]	Negative

TABLE 2—*Concluded*

PATIENT	DIAGNOSIS	FLUID			TEST			REACTION	
		Source	Guinea pig inoculation	Smear for tubercle bacilli	Guinea pig number	Amount of fluid injected	Days	Right testis	Left testis
						cc.			
Wo.	Bronchiectasis	Pus from lung abscess	−	−	208(Tb+)R	0.2	5	Marked degeneration, comparable to positive reaction	
					L	0.05	5		Degeneration as in right testis, only in less degree
					232(Tb−)L	0.2	5	Negative	[Negative]
C. H.	Hypertension and cardiac failure	Pleural cavity at autopsy	−	−	198(Tb+)	0.1	5	Marked degeneration, easily passing for positive reaction	Negative
					153(Tb−)	0.1	5	Negative	Negative
Bi.	Cyst of tibia	Cyst	−	−	117(Tb+)	0.1	5	Negative (one section shows some toxic degeneration)	Negative
					213(Tb−)	0.1	5	Negative	[Negative]

* Fluid kept 10 days in refrigerator before use.

We know also that bacterial contamination of the fluid, of itself, was not active in producing the reaction, for several fluids which were heavily contaminated with staphylococci, streptococci, and other microörganisms usually gave no reaction in the sensitized or nonsensitized testis.

In addition, sterile Berkefeld filtrates of 48-hour broth cultures of *Streptococcus viridans* and *Staphylococcus aureus* produced at the most only a slight washing out of spermatozoa in 1–2 per cent of the tubules when injected in amounts of 0.1 and 0.2 cc. The *Streptococcus viridans* had recently been isolated from a lung abscess, and was markedly pathogenic for guinea pigs.

Proteins and split-proteins had no effect upon the testes of tuberculous guinea pigs. Albumin and globulin were prepared from normal human serum, and made up in sterile salt solution to approximately the same concentration as found in synovial fluid. The solution was filtered through a sterile Berkefeld filter. The biuret test showed the absence of products of protein decomposition. One-tenth cubic centimetre of this protein solution caused no reaction when injected into the testes of tuberculous and nontuberculous guinea pigs.

The protein solution above described was digested with trypsin. After the addition of sterile 2 per cent trypsin, the mixture was incubated at 37°C. for four days; the biuret test at this time indicated the presence of products of protein decomposition. This solution produced no degeneration in the testes of tuberculous and nontuberculous guinea pigs, when injected in amounts of 0.1 cc. The same volume of a corresponding dilution of trypsin in salt solution likewise had no effect upon the testes of tuberculous and nontuberculous animals. At the most, in both cases, there was only a slight washing out of spermatozoa in less than 1 per cent of the tubules.

It was thought that the specific nature of the reaction might be more clearly brought out, and the diagnostic value of the test increased, by working along quantitative lines, and reducing to one-half or one-quarter the amount of fluid injected, thus eliminating the toxic effects, while the specific effect would remain. However, a study of the tables will show that, while as little as 0.05 to 0.03 cc. of tuberculous fluid from joints or abscesses will usually give a positive reaction, one spinal fluid was encountered which gave a negative reaction when 0.1 cc. was injected (*Hu.*). Further, of three nontuberculous and noncarcinomatous fluids giving a positive reaction, two (*Wo., H.H.*) produced typical degeneration, even when injected in amounts of 0.05 cc., indicating the difficulty

TABLE 3

Fluids from cases of malignant tumor

PATIENT	DIAGNOSIS	FLUID			TEST			REACTION	
		Source	Guinea pig inoculation	Smear for tubercle bacilli	Guinea pig number	Amount of fluid injected	Days	Right testis	Left testis
						cc.			
H. C.	Carcinoma of lung	Pleural cavity	−	−	127(Tb+)	0.1	5	25 per cent degeneration	Negative
					154(Tb−)	0.1	5	10 per cent degeneration	Negative
Ja.	Carcinoma of lung	Pleural cavity	−	−	77(Tb+)	0.2	8	25 per cent degeneration	Negative (Testes immature. Tubercles between testis and epididymis)
					430(Tb−)	0.2	4*	Negative	Negative
A. R.	Carcinoma of lung	Pleural cavity	−	−	105(Tb+)	0.1	5	70 per cent degeneration	Negative
					150(Tb−)L	0.1	5	[Negative]	3 per cent degeneration
S. G.	Carcinoma of ovary	Abdominal cavity	−	−	137(Tb+)	0.1	5	30 per cent degeneration	10 per cent degeneration (testes immature)
					167(Tb−)R	0.1	5	3 per cent degeneration	[Negative]
T. C.	Carcinoma of breast; metastasis to ovary	Abdominal cavity	−	−	138(Tb+)	0.1	5	Negative	Negative
					167(Tb−)L	0.1	5	[Negative]	Negative
A. L.	Intraäbdominal malignant tumor	Abdominal cavity	−	−	158(Tb+)	0.1	5	Negative	Negative
					174(Tb−)	0.1	5	Negative	Negative

Bel.	Hypernephroma of kidney; metastasis to lung	Pleural cavity	−	−	181(Tb+)	0.1	5	Negative	Negative
					210(Tb−)R	0.1	5	Negative	[Negative]; 7 to 10 per cent degeneration; fluid M. S.
M. S.	Papillary adenocarcinoma of ovary; metastasis to peritoneum	Abdominal cavity	−	−	188(Tb+)	0.1	5	10 per cent severe degeneration; 30 per cent moderate degeneration	Negative
					210(Tb−)L	0.1	5	[Negative]	7 to 10 per cent degeneration

*Died of intercurrent infection.

of reducing the nonspecific effect of these fluids if the toxic material is present in concentration. Unfortunately none of the fluids from cases of malignant tumor was tested quantitatively. As yet a sufficient number of experiments to evaluate the quantitative factor has not been done, and the practical application of this method as a method of diagnosis of tuberculosis probably hinges on this factor. Conversely, with tuberculous fluids we have found that the positive response may be eliminated by too great dilution; therefore we can only summarize our work in this regard by indicating that it may be difficult to eliminate sometimes a toxic nonspecific effect, while, on the other hand, a definitely specific effect may be lost by dilution.

DISCUSSION

Our results would indicate that there is a considerable specificity of reaction with tuberculous fluids. One of our tuberculous fluids, a spinal fluid, gave no reaction when inoculated (0.1 cc.) into the testis of a tuberculous guinea pig, and induced only a few extremely sclerotic tubercles in the spleen after eleven weeks, when 3 cc. of the fluid were injected into a diagnostic guinea pig. Since the spermatocyte reaction is dependent upon tuberculin or tuberculotoxic material in the fluid, it is clearly seen that these substances, while present, could easily have been considerably diluted, for the cerebrospinal fluid is in circulation, passing after its production by the arachnoidal plexuses into the general circulation. The accumulation of toxic material then is reduced to a minimum. The infectivity of the fluid itself was not great because only a few tubercles in the guinea pig were present about three months after the injection of the fluid.

The adaptability of this procedure for the diagnosis of tuberculous meningitis, we believe, is not feasible, though our experience is very limited. We have found that when the fluids have been confined to body cavities, such fluids are best suited for eliciting a positive spermatocyte reaction. We have also in a rough way found a certain parallelism between the severity of the spermatocyte reaction and the virulence of the tuberculosis induced in the diagnostic guinea pig on the subcutaneous inoculation of fluids. There is an additional factor to be considered in evaluating the results obtained with tuberculous fluids from closely confined cavities, and this is that the tuberculous specific effect may be enhanced by a toxic factor developed in the fluid due to its confinement. This toxic nonspecific effect is indicated by the fact that such fluids may

induce a certain amount of degeneration in the testes of nontuberculous guinea pigs, but it is most emphatically demonstrated when fluids, known to be nontuberculous, induce a degeneration of the testis indistinguishable from the typical spermatocyte reaction when inoculated into the testis of a tuberculous animal, and also cause a degeneration of the testis of a nontuberculous guinea pig. When these nonspecific toxic reactions were elicited, it was constantly true that the degeneration in the testis of the tuberculous animal was more severe than that in the nontuberculous animal.

This indicated to us that the degenerative response produced by nontuberculous fluids was related to the sensitivity of the testis, and that the threshhold of sensitivity to toxic effects was diminished in tuberculous guinea pigs. It is doubtless true that the "spermatocyte reaction" may be entirely specific when dilutions of Old Tuberculin or culture filtrates are injected into the testes of properly prepared animals, as has been done experimentally with guinea pigs sensitized by tuberculosis, blastomycosis, *B. abortus* infection, or coccidiosis (4) (5); but from the work we have reported it is apparent that, when applied to body fluids, the specificity of the test is diminished by the possibility of some inherent toxicity of the fluid. As a matter of fact, we found that concentrated Old Tuberculin possesses a sufficient toxic effect to produce marked degeneration of the testis of a normal noninfected (and nonsensitized) guinea pig when injected in amounts of 0.1 cc.; the same volume of a dilution of Old Tuberculin as low as 1:10 has no effect whatever upon the testis of a normal guinea pig. The same thing is true in the case of normal albino rats (3). Furthermore, tuberculous fluids, which brought about nearly complete destruction in the testes of tuberculous guinea pigs, very occasionally caused degeneration of 3–10 per cent of the tubules in nonsensitized animals, thus pointing again toward toxicity of the fluids as a factor in causing the reactions we have described.

It was also found that fluids which came from carcinomatous foci, or other foci where considerable tissue destruction had occurred, gave in about 35 per cent of the cases some degree of degeneration in the testis of a tuberculous guinea pig, sometimes quite severe, and then indistinguishable from the effect obtained with a tuberculous fluid. This was a toxic effect because these fluids occasionally produced a certain amount of degeneration in the testes of nonsensitized guinea pigs.

Our interest in developing this method has been to aid us in making a diagnosis of tuberculosis on joint fluids, so that the presence of tubercu-

lous synovitis or osteitis could be shown. The presence of tuberculosis of bones or joints has always been a diagnostic difficulty, and the diagnosis is sometimes never established with certainty. Any results based purely on the clinical diagnosis of tuberculosis of bones and joints cannot be accepted in their entirety, for, while most of such cases are tuberculous, many are caused by other microörganisms. There are some who are extreme in their belief that all these cases should be explored, and a piece of the synovial membrane be subjected to pathological examination. Any pathologist with experience with joint tissues will appreciate the difficulties which exist in the making of a diagnosis on a piece of tissue removed at biopsy because of the frequency with which a part of the membrane may be thickened and show no other disease but simple inflammation. At this time it is important to emphasize that tuberculous joints may be affected in different ways in different individuals, depending upon the virulence of the tubercle bacillus and the resistance of the individual, and possibly other unknown factors that are at work in this disease. It should also be pointed out that while tuberculin and tuberculotoxins are produced as a result of the activity of the tubercle bacillus in the body, it is conceivable that different strains of tubercle bacilli may produce tuberculins and tuberculotoxins of varying strength, so that the fluids from one joint, although tuberculous, may give a weaker response than a corresponding amount from another individual. This factor would indicate that the spermatocyte response may even be varied for this reason. Another problem that warrants much further investigation is the question of nontuberculous acid-fast infections of joints.

SUMMARY

In summary, an attempt was made to apply Long's "spermatocyte reaction" (testicular tuberculin reaction) to the diagnosis of body fluids suspected of coming from tuberculous foci. The test consists of the injection of 0.1 to 0.3 cc. of the suspected fluid into the testis of a tuberculous guinea pig, autopsy of the animal after five to seven days, and histological examination of the testis for a characteristic degeneration. The diagnostic value of the test is impaired by the fact that rarely a tuberculous fluid failed to give the typical reaction, and about 35 per cent of nontuberculous fluids (particularly fluids from cases of malignant tumor) gave a reaction which was histologically indistinguishable from that given by a tuberculous fluid. Data obtained show that this is a toxic effect, which apparently cannot be eliminated by reducing the

amount of fluid injected. However, it may be said that, with the exception of spinal fluids, if 0.1 to 0.2 cc. of a fluid from a suspected tuberculous focus, upon inoculation into the testis of a tuberculous guinea pig, produces no reaction as above described, the possibility of tuberculosis of that focus may be definitely ruled out.

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THE COMPRESSION THERAPY OF PULMONARY TUBERCULOSIS

A Comparative Study

LEROY S. PETERS

The treatment of pulmonary tuberculosis by those various methods at our command that tend to restrict the movements of the diseased lung is no longer in the experimental stage. It is especially true in the field of artificial pneumothorax that we have many men with large experience and sufficient cases to afford us valuable statistics and to give us information that places this form of compression on a safe and sound basis. It is becoming equally true in the matter of major surgery. Extrapleural thoracoplasty, in the hands of competent surgeons, becomes less of a risk yearly, and to-day can be placed with artificial pneumothorax as a legitimate method of lung compression.

We all recognize the value of rest in the treatment of active tuberculosis. It is this fact that has led to the employment of various devices to control movement of the diseased lung. Such appliances as pneumatic splints, hard pillows, bricks to the affected side, adhesive straps, have had or are still having their vogue, and many physicians as well as patients are loud in their praise. They show you how cavities have been healed, and how extensive tuberculosis has been arrested through the use of this or that particular form of external appliance. We can show you the same results without it. The value of this type of compression lies in the fact that if a patient is devoid of a nervous system, and can lie for hours on a hard pillow, he or she is simply following out a rigid rest cure, and the end-result is due to bodily rest rather than rest of the affected part. Compression therapy to be effective must compress. Witness the brilliant results in pneumothorax when the collapse is complete, and the far less satisfactory ending when adhesions prevent a perfect compression. To satisfy ourselves on postural rest, a patient was placed on a hard pillow and kept on his side for six hours. In the beginning the diaphragm on the lower side had an excursion of $2\frac{1}{2}$ to 3 inches, and the upper diaphragm remained practically stationary. At the end of two and one-half hours the excursion was about equal in both

sides, but at the end of six hours the dependent diaphragm moved fully an inch more than did the one in the uppermost sides.

The principal reason for our opposition to the less effective methods lies in the fact that much valuable time is wasted, and often the disease progresses unfavorably to the point where more effective means are contraindicated. It is true, however, that no patient should be rushed into this type of therapy. If we are to keep lung collapse on a sane basis, great care and caution should be exercised by the physicians doing tuberculosis work. Nature should be given her chance under close observation, and many times Nature succeeds. This we shall attempt to show later. The point that should be kept in mind is that in compression therapy we have a real adjunct in the treatment of a very stubborn disease, and the patient is most fortunate who presents himself as a suitable type of case. It is to be deplored that not more than 10 per cent are favorable risks, for by this means we more than triple the chances to effect an arrest of the process.

We can divide the methods at our disposal into three types of compression: (1) phrenectomy, (2) artificial pneumothorax, and (3) extrapleural thoracoplasty.

Under artificial pneumothorax we mention, as a subhead, the cauterization of adhesions after the method of Jacobaeus. Let us discuss these methods separately.

Phrenectomy: Many men do phrenectomy, as a routine measure, prior to thoracoplasty. This no doubt increases the volume of compression, but as a factor in determining the ability of the contralateral lung to hold up under a thoracoplasty it is of questionable value. The extra burden thrown upon the opposite side is too slight to affect it unfavorably.

A phrenectomy, to be effective permanently, requires the removal of a large part of the nerve,—we try to get at least 8 to 10 inches, and, if possible, remove it entirely. This can be accomplished, as we have demonstrated a number of times on the cadaver. If only a small amount is removed, the nerve regenerates, with a restoration of diaphragmatic function. With the diaphragm paralyzed, it is raised two to three inches and produces an excellent compression of the lower lung. We have compressed cavities perfectly in the lower third of the lung by this method, and have had perfect arrests of cases with basal lesions without resorting to other forms of compression. It is also surprising to see how much compression is produced on the entire volume of the lungs. For that reason we have removed the nerve when artificial pneumothorax was impossible

because of adhesions and the patient had too much trouble in the contralateral lung to permit of more radical surgery. Marked improvement has been noted in a number of such cases. The operation is harmless, and with proper surgical technique the scar is negligible. The field, as far as compression results are concerned, is limited, and as a method *per se* phrenectomy should be restricted to basal lesions. It can in no other type of case replace the more efficient forms of compression.

Artificial Pneumothorax and Thoracoplasty: After sixteen years' experience with artificial pneumothorax we are convinced that it is by far the best method when a good collapse is obtained. When adhesions that are not operable prevent perfect collapse, a thoracoplasty, without question, gives a far more satisfactory result. Someone has phrased the comparison very aptly: "A good pneumothorax is better than a thoracoplasty, but a thoracoplasty is better than a poor pneumothorax." There are some phthisiotherapists, as well as some chest surgeons, who

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FIG. 1. Basal lesion of right lung; 12 years' duration; repeated febrile attacks from plugged drainage. Phrenectomy done two years ago, and patient well since.

FIG. 2. Same as fig. 1 after phrenectomy.

FIG. 3. Extensive bilateral tuberculosis.

FIG. 4. Same as fig. 3 after 6 months' rest.

FIG. 5. Mediastinal hernia, due to injections of 1000 to 1600 cc. of air three times weekly. With no injections for a period of 2 months the air was absorbed.

FIG. 6. Pneumothorax case, showing what seemed a burnable adhesion. The apparent adhesion proved to be the floor of a cavity. An attempt to cauterize resulted in a natural pneumothorax after a week's time.

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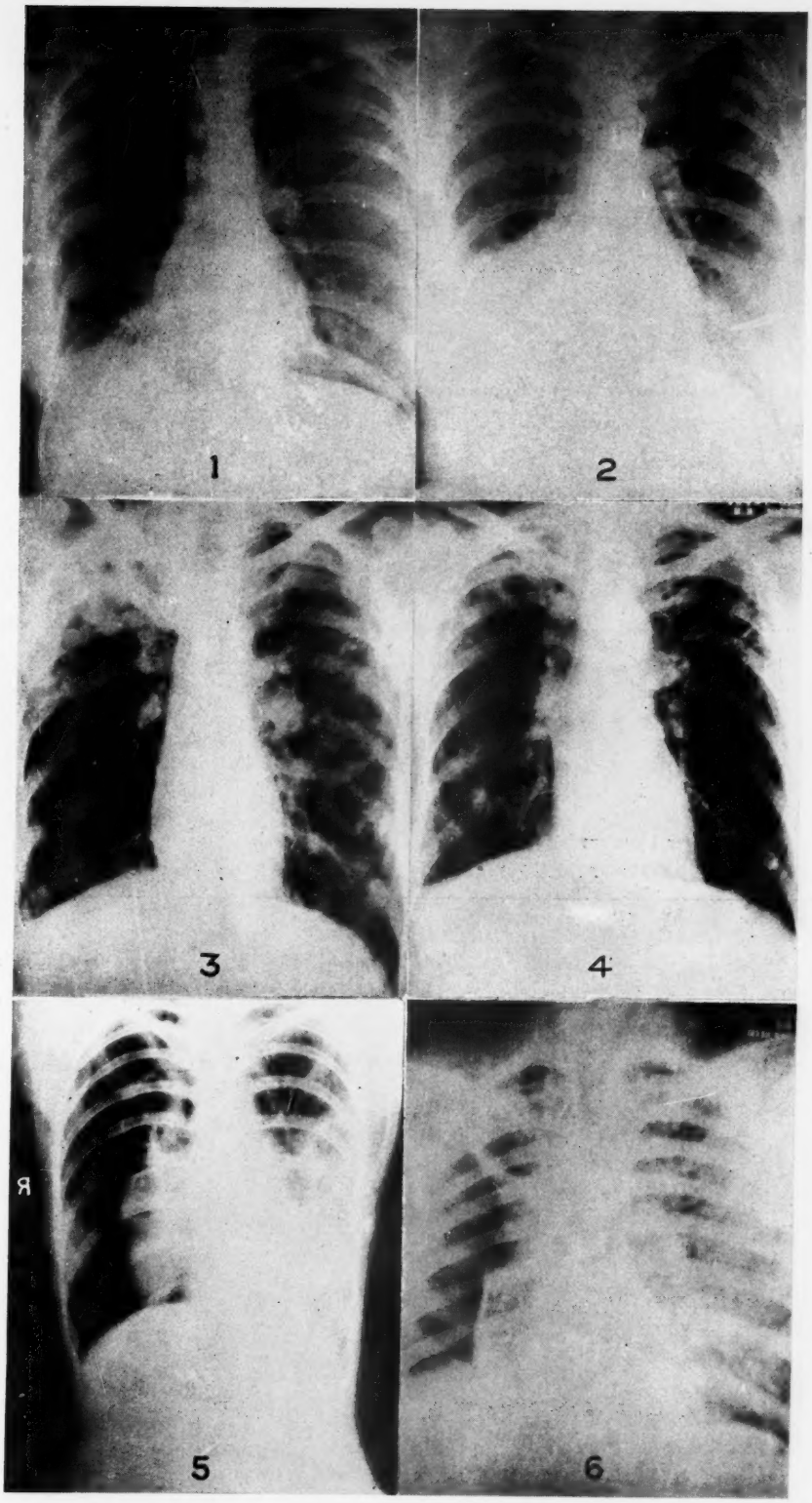
advocate rib-resection in lieu of pneumothorax, claiming that once the operation is over the patient is through and his troubles are ended, the need of refills is past history, the danger from the terrible bugaboo, empyema, is no longer present, and the unsuspecting victim is translated to a Utopia where life becomes an asset rather than a liability. If this were true, there would be no argument, but an argument is still in order. The world is still the unhappy arena of lung specialists who never learn, and in their hands the results in artificial pneumothorax are disappointing. However, many surgeons who have had no experience in chest surgery are posing as specialists in that field, and the results necessarily in their hands are equally disappointing. But as long as we have the human equation with which to deal, it will be difficult to remove this complication.

Other complications in pneumothorax are so infrequent as to be in-



FIGS. 1–6

consequential. There is less than one per cent of progressive cases in which bilateral disease exists in "good-collapse" patients. There is only 4 per cent of progressive cases in "poor-collapse" patients. Exudates occur in 70 per cent of all cases under compression, and 20 per cent of these develop pus, but only 7 per cent show mixed infection, or a true empyema. We can disregard the serous fluids and the pus caused by the tubercle bacillus, since no ill effect is seen except when the fluid rises high enough to cause pressure symptoms, in which case it can be removed. True empyema is serious, but offers a 50 per cent chance of cure by thoracoplasty. When it does occur, it is caused by a natural pneumothorax, and this accident is no more common in artificial pneumothorax than in the general run of tuberculosis. Some time ago we had eight cases of natural pneumothorax and six of them never saw a gas needle.

FIG. 7. Same as fig. 6 after pneumothorax and a resulting empyema. Thoracoplasty produced a perfect result.

FIG. 8. Pneumothorax case with adhesion over upper right which was cauterized. Note cavitation in pneumothorax lung at root.

FIG. 9. Same as fig. 8 after cauterization. Excellent compression with cavities closed.

FIG. 10. Cavity in left apex of 2 years' standing. Repeated febrile reactions due to plugged drainage.

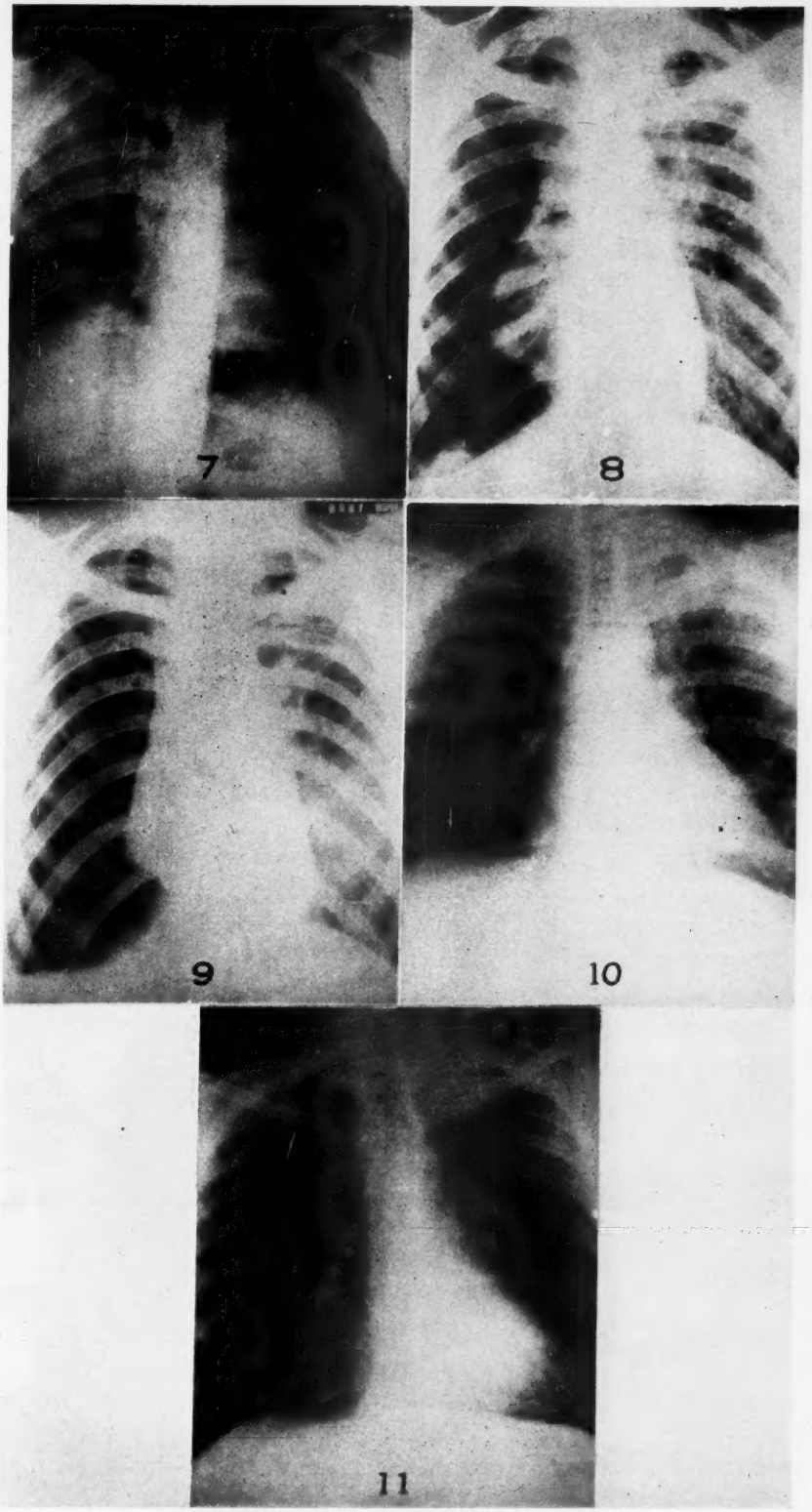
FIG. 11. After 1½ years in Southwest, the last year of which has been spent leading a normal life. Temperature normal over a year.

After a year's treatment the refills are not troublesome. The intervals are so far apart that they cause no inconvenience. We have many patients working who report for refills, and return to work with very little loss of time.

Again, if the contralateral lung becomes active, treatment can be stopped. This is not true of radical surgery. A thoracoplasty once done is done forever, and an activation of the opposite lung spells disaster.

Then too, if one feels the necessity, a pneumothorax can be kept up for life, and, if the collapse is perfect, it offers a longer period of normal health than does a thoracoplasty.

One must never lose sight of the fact that to do a thoracoplasty is to perform a major operation, and that, too, on an individual who, from the standpoint of operative interference, is a poor surgical risk. Many of these patients die of cardiac failure from the operation alone, and many



FIGS. 7–11

die from activation in the contralateral lung, not to mention such complications as nephritis, intestinal tuberculosis, miliary extension resulting in meningitis, all lighted up probably as a result of lowered resistance from operative interference. Not infrequently a bronchopneumonia develops from the aspiration of purulent material from the diseased lung, and in practically all cases this proves fatal. Mediastinal flutter and paradoxical breathing are not to be forgotten. Weigh all these against the complications of pneumothorax before you gain the impression that it should be the operation of choice.

A good collapse can be obtained in 39 per cent of all patients, while 33 per cent show only a partial compression. A few of the latter can be converted into the former by the cauterization of adhesions after the method of Jacobaeus. Our experience has been limited, but, when on exploration we have found the right type of adhesion, results have been brilliant. Broad bands are dangerous because of the fact that so often they contain lung, and to burn through them invites a natural pneumothorax with a complicating empyema. Nor does the X-ray always give definite proof of the burnable type; only by inspection with the thoracoscope in the chest can one be reasonably sure, and if not certain it is far better to withdraw gracefully.

If cauterization cannot be done, it is useless to continue pneumothorax treatment indefinitely, with the idea of stretching adhesions, or of breaking through them with high pressures. This is not only a mistake but a dangerous procedure, and one that careful operators will not practise. If the contralateral lung is reasonably safe, thoracoplasty should be advised before the patient becomes too ill to be a good surgical risk.

We are opposed to an upper-stage thoracoplasty with a continuation of pneumothorax treatment. If a thoracoplasty is indicated, do a complete operation unless occasionally a phrenectomy might be done when it is desirable to save the lower lung in case it is not diseased.

Tables 1 to 4 give our end-results in 700 cases of artificial pneumothorax, in 36 cases of thoracoplasty, and in 40 cases of phrenectomy. The first series of 273 cases was reported in 1919, and the records lost in a fire at the Albuquerque Sanatorium. These were not classified from the standpoint of good and partial collapse. It is interesting to note, however, that the results in the 427 cases chosen and treated in later years are better than in the first series, which is due, no doubt, to a better selection of cases. The percentage of fluids remains about equal in both series. We see little difference in the percentage of free plereral space, and the deaths are about the same in both.

TABLE 1

A

First series: 273 cases

CLINICALLY WELL	DEAD	NO FREE PLEURAL SPACE
31 per cent	44 per cent	30 per cent

B

Second series: 427 cases

	CLINICALLY WELL		DEAD		BILTERAL DISEASE PROGRESSIVE	
	Cases		Cases		Cases	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*
Good collapse 167 cases, 39 per cent*.....	89	53	41	24	9	1
Poor collapse 140 cases, 33 per cent.....	36	25	63	44	57	4
No free space 120 cases, 28 per cent.....	20	16	74	60		
Total: 427 cases, 100 per cent.....	145	34	178	42	66	15

*The apparent discrepancy in the total number of cases is due to the fact that a number of the progressives are also among the number of the dead.

TABLE 2

	FLUIDS		PUS		MIXED INFECTION	
	Cases		Cases		Cases	
	number	*per cent*	*number*	*per cent*	*number*	*per cent*
First series, 273 cases.....		66		22		9
Second series, 427 cases.....	304	70	61	20	27	7

TABLE 3

	CLINICALLY WELL	DEAD
Thoracoplasties, 36 cases.....	13 or 36 per cent	15 or 42 per cent

TABLE 4

PHRENECTOMIES	CLINICALLY WELL	IMPROVED	DEAD
Basal lesions, 3 cases.....	3		
Entire lung, 15 cases.....		2 or 13 per cent	1 or 7 per cent
Preliminary to rib-resection; 20 cases.....			
Supplementary to thoracoplasty to close cavity, 1 case.....	1		
Supplementary to upper rib-resection, 1 case....	1		

You will note we have used the classification *Clinically well.* This comprises all patients who are working or otherwise leading normal lives. They may or may not have tubercle bacilli in the sputum. The term *Cure* or *Arrest* should be eliminated. It really spells nothing. Many cases classified as *bacilli-free,* if followed closely, will at times show positive sputum, and this is especially true in advanced disease such as we are dealing with in compression patients.

It will be noted from the tables that a complete collapse by artificial pneumothorax offers the best results. There are 53 per cent clinically well and only 24 per cent dead, as compared to 25 per cent clinically well and 44 per cent dead in the partial-collapse series. The cases of bilateral disease show less than 1 per cent progression in the case of complete collapse, while 4 per cent are progressive in the partial-collapse group.

Comparing the pneumothorax with thoracoplasty, we find that more radical surgery offers a better result than does partial pneumothorax, but it does not compare favorably with the "good-collapse" pneumothorax. The percentage of the dead among rib-resection cases is practically the same as in those with partial collapse, due no doubt to the fact that, lacking a complete compression, the toxins of tuberculosis are not as well cared for as after a good collapse.

CONCLUSIONS

1. A patient should be placed under observation at bed-rest to see what can be accomplished before advising any form of compression therapy.

2. External appliances, such as pneumatic splints, hard pillows, etc., should not be used indefinitely in lieu of the more effective forms of compression.

3. Phrenectomy is effective only in basal lesions and as a preliminary to thoracoplasty.

4. Artificial pneumothorax is the most efficient of all forms of compression when a good collapse is possible.

5. Thoracoplasty is indicated when a pneumothorax cannot be done, or when the collapse is only partial and cannot be made effective by cauterization after the method of Jacobaeus.

6. The complications of pneumothorax are so few and their percentage so small as to be negligible.

7. Thoracoplasty is a major operation, and tuberculous patients are poor surgical risks.

8. It is a mistake to attempt to stretch adhesions or break them by high pressures, and to continue this indefinitely, with the hope of ultimately getting a collapse, is a most dangerous procedure.

9. There is no reason for doing an upper-stage thoracoplasty and supplementing this with a pneumothorax.

10. Thoracoplasty offers a better end-result than a partial pneumothorax, but does not compare favorably with a complete pneumothorax.

I wish to express my appreciation to Dr. P. G. Cornish, Jr., who does my chest surgery and whose coöperation makes possible the surgical results.

BLOOD TRANSFUSION IN PULMONARY TUBERCULOSIS

Case Reports

W. G. GAMBLE, JR.[1]

Blood transfusion, like patent medicines, has been advocated for almost every ill of the human race. Yet little has been said about its therapeutic effect in tuberculosis. As a life-saving measure after haemorrhage, as an aid to combat the anaemia of the disease, and as a means of promoting nutrition, it has a definite place in the treatment of tuberculosis.

Presented below are four selected case histories, illustrating different types of tuberculosis in which transfusion was used. These are necessarily brief and contain only main essentials.

Case 1: C. L., white male, 18 years, football player. History of injury to knee two years previously. Family and personal history unimportant. Physical examination discloses moderately advanced left-sided pulmonary tuberculosis. Has swollen left knee-joint, decided to be tuberculous after clinical and X-ray examinations.

General and local treatment instituted, ten days after adminission on account of anaemia and poor appetite; 300 cc. of blood given. Transfusion repeated on 25th day. Clinical improvement very slight after the first transfusion, but marked after second. Later discharged with condition improved and advised to go to sanatorium.

Progress record

DATE	HAEMOGLOBIN	ERYTHROCYTES	TRANSFUSION	REMARKS
	per cent		*cc.*	
1/ 5/26	50	3,200,000		Patient weak; poor appetite; psychic reaction; downcast
1/10/26	45		300	Not nervous; temperature slightly raised
1/15/26	48	3,500,000		Very little improvement; temperature about same
1/25/26	55		300	More cheerful
1/30/26		3,410,000		Appetite improved; clinical improvement.
2/10/26	60	3,500,000		Improving
2/17/26	60	3,548,000		Gain in weight; cheerful; good appetite; advised to enter sanatorium

[1] Medical College of South Carolina, Charleston, South Carolina.

Case 2: A. L., male, colored, 28 years, with usual signs and symptoms of pulmonary tuberculosis in right lung. Eight months after diagnosis patient had large haemorrhage; brought to hospital in poor condition; presented symptoms of acute anaemia. Second day in hospital haemorrhage ceased. Three transfusions of 300 cc. each given; did not cause any excitement. Patient relieved and appetite improved. There was no tendency for haemorrhage to take place as result of transfusion. Patient left hospital with general condition good. Died six months later on account of neglect.

DATE	HAEMOGLOBIN	ERYTHROCYTES	TRANSFUSION	REMARKS
	per cent		*cc.*	
5/ 6/25	40	3,600,000		Poor condition; respirations fast; temperature high; clammy
5/ 6/25	40		300	Better; acute symptoms relieved. Haemoglobin immediately afterward, 43 per cent. Blood-pressure rose from 106/60 to 114/68
5/ 9/25	45	3,750,000		Appetite improving; mental outlook better
5/10/25			300	No change
5/15/25			300	Patient improving
5/25/25	68	4,350,000		Clinically better; gain in weight; temperature slightly lower

Case 3: I. S., colored male, age 17. Diagnosis of purpura haemorrhagica; pulmonary tuberculosis. Complains on admission of bleeding from teeth, nose and rectum; black urine and stools; fainting spells and vomiting black blood. Family and previous history unimportant, except for obscure illness two months ago. For the first ten days rapid pulse and high temperature. Blood-pressure 112/58, 116/56, 100/70, 112/50 and 110/62.

Physical examination: Pulse 128, temperature 99. Head and neck negative with exception of haemorrhage and ecchymoses in and from nose, tongue, lips, gums, eyes, and chest. Coarse râles along medial border of scapula. Cardiovascular, abdomen and external genitalia apparently normal. Numerous cutaneous ecchymoses all over body.

Laboratory findings

DATE	ALBUMIN	CASTS	BLOOD	REMARKS
1/11/27	3 Plus	One plus	4 Plus	
1/12/27	3 Plus	0	4 Plus	Received 320 cc. of whole blood
1/16/27	2 Plus	0	4 Plus	Received 300 cc. more blood
1/18/27	0	0	0	Urine from then on apparently normal

Wasserman and Kahn tests negative. Blood-cultures negative. Sputum negative, 1/22/27 and 2/29/27; positive for tubercle bacilli, 2/4/27.

This case is reported in some detail on account of the relatively rare occurrence of purpura haemorrhagica before a diagnosis of tuberculosis is made. It was at first treated with calcium, horse-serum and various other measures. When these were without effect transfusion was used, with improvement.

DATE	HAEMOGLOBIN	ERYTHROCYTES	LEUCOCYTES	TRANSFUSION	REMARKS
	per cent			*cc.*	
1/11/27	30	2,000,000	16,000		Clinical condition poor; bleeding time 16 minutes; coagulation time 9 minutes; blood-platelets 25,000
1/12/26	30			300	Blood-pressure from 110/60 to 108/70. Haemoglobin rose to 33 per cent. Prothrombin time from 20 to 18 minutes. No change clincially except patient more cheerful.
1/13/26	28	2,175,000	16,050		Still bleeding
1/14/27	24			500	Still bleeding; respiration fast; no rise in blood-pressure after receiving blood; patient is clinically better
1/16/27	36	2,776,000			Platelets 163,000; symptoms improved; appetite better
1/18/27	46	2,970,000	12,020		Bleeding from mucous membranes ceased on evening of 16th
2/ 1/27	55	3,400,000	10,040		Coagulation time 7 minutes; bleeding time 3 minutes; improved clinically; appetite good
2/23/27	70	4,000,000	10,220		Platelets 170,000; 43 days after admission patient was much better, but pulmonary tuberculosis was discovered, so he was transferred to tuberculosis sanatorium where he is, and has good chance for recovery.

Case 4: L. S., white, male, age 30 years, medical student. Developed severe pulmonary tuberculosis in early part of 1924. Gradually lost ground in spite of institutional treatment for two and a half years.

Whole left lung was involved, August 16, 1926; cavity-formation; has had repeated haemorrhages; advised to undergo thoracoplasty.

DATE	HAEMOGLOBIN	ERYTHROCYTES	TRANSFUSION	REMARKS
	per cent		*cc.*	
8/16/26	70	3,300,000		First stage of operation performed; in poor condition; poor mental outlook
8/17/26	52	2,500,000	500	Haemoglobin after transfusion 58 per cent; blood-pressure from 120/60 to 118/68; red cells rose 100,000; prothrombin time from 10 to 6 minutes; temperature 99 to 98; pulse 100; respiration unchanged
8/18/26	65	3,120,000		Appetite improved; more cheerful; temperature 99; pulse and respiration same
8/19/26	65	3,300,000		Second stage of operation; stood it fairly well
8/21/26	60	3,000,000		Fair condition
12/14/26				Has had two large haemorrhages; mental outlook poor
12/15/26	55		500	Patient developed slight reaction with urticaria; blood-pressure from 118/20 to 122/60; fair appetite; haemoglobin afterward 58 per cent; patient had returned to sanatorium
12/20/26	72			Spirits good; appetite better
12/25/26				Had large haemorrhage; also on 12/30/26, 1/5/27, and 2/1/27
2/ 6/27	50		500	Haemoglobin afterward 52 per cent; blood-pressure from 100/54 to 1/2/64; pulse 120 to 100; temperature 100 to 99; respiration 26 to 27
2/10/28	75			Patient feels better; no more haemorrhages. Appetite better; is more cheerful. On 3/25/27, the patient still living though both lungs are involved and has many depressing accidents. Allowed to go on furlough
6/ 7/28			840	While home on account of haemorrhages, was given blood; cheered him up and he felt better
6/16/27			300	Had a reaction; was transfused on account of haemorrhages; has had no tendency to bleed
3/26/28				Patient still living in spite of condition

These selected cases illustrate the use of whole-blood transfusions in average cases of tuberculosis. No extraordinary therapeutic effects need be expected, yet the prognosis is much better when the above measure is used.

We do not advocate transfusing every case of tuberculosis, even if such were possible. In this, as in other conditions, we should select our cases. It is not advocated during or immediately after large pulmonary haemorrhages, for reasons self-evident; after the lapse of a few hours, the writer believes that this operation is safe and justifiable. The

happy, cheerful disposition of a patient suffering from tuberculosis is familiar, but the most optimistic patient gets a sudden jolt when he has a large haemorrhage. We get a good psychic reaction in giving blood, for "we replace that which he lost."

What may be the effect of decreasing the clotting and prothrombin times on small haemorrhages, in tuberculous individuals, we cannot say. In other conditions it is of apparent value.

According to some books, 500 cc. of blood introduced into the vein will materially change at once the haemoglobin and erythrocyte count. This laboratory has not found this to be the case. There is an immediate temporary rise in the haemoglobin of from three to five per cent. After a day both haemoglobin and erythrocyte counts begin to rise slowly.

The appetite after transfusion is usually improved. Perhaps some of the clinical, as well as laboratory results, are due as much to this as to the immediate effect of the donated blood. But, irrespective of whether this is the primary or secondary cause, we get the patient to eat, and this, to be trite, is worth while. In passing, it is well to mention that an increased appetite is the usual result in other cases.

Transfusion has been objected to, as it is said that it will cause a rise in the blood-pressure, hence there will be a greater tendency toward haemorrhage. This is not the case; the maximum rise was not over 10 mm. Hg. In many individuals there was no rise, provided the patient was not suffering from renal or generalized arteriosclerosis.

In most individuals, there is at first a slight nervous apprehension as this measure is new to them. This in tuberculosis might be dangerous; so it is avoided by giving 0.5 gr. of morphine before starting. This is effective in alleviating coughing spells.

This measure has a financial side, speaking of local conditions. In our series, it is estimated that one pint of blood will shorten the patient's stay in the hospital about 14 days. The usual expense averages about $40.00 a week, and a transfusion, provided the physicians services are free, and the blood is bought, costs $25.00. Thus we have an economic gain.

Reactions demand some attention. During the last four years in over 600 cases our reactions have been few. But we have them occasionally, like every one else. And most of them we do not think are due to errors in typing. We have noted that they are more frequent in three classes of cases, in septicaemias, pernicious anaemia and tuberculosis. We are

not as yet entirely satisfied as to their cause in tuberculosis, and will not venture an opinion. They are all mild in this condition, and usually urticarial in type. They do not constitute a contraindication.

CONCLUSION

Transfusion in selected cases of pulmonary tuberculosis provides a means of building up the patient's blood, with resulting mental, physical and economic gain.

REMARKS ON TUBERCULOUS PLEURISY, ESPECIALLY ITS TREATMENT

E. S. BULLOCK[1]

Pleurisy, like pulmonary haemorrhage, must always be considered tuberculous until proved otherwise, and it is only tuberculous pleurisy that is considered here. It has long been known that persons complaining of pleuritic pain and nothing else will subsequently prove to be frank cases of pulmonary tuberculosis. The term *idiopathic pleurisy* is obsolete, though the aetiology of both dry and wet pleurisy in childhood, before the fifteenth year, still remains somewhat obscure, as pulmonary tuberculosis seldom follows this affection in children, who seem to possess a substantial immunity to progressive pulmonary disease, even though careful anatomical studies by many investigators, among whom Ghon of Vienna is the outstanding figure, show that among children in a large city dying of other diseases a primary tuberculous focus in the lung can be demonstrated in a very large proportion, either active or retrogressive, or already healed with secondary tuberculous infection of the tracheobronchial lymph nodes. Bearing this in mind, the dry and wet pleurisy of children, so seldom followed by progressive pulmonary disease, is probably of tuberculous origin.

In some cases, but not all by any means, a wet pleurisy has a wonderful effect upon the underlying tuberculosis. As an example, let me cite the case of a patient of mine who conceived the brilliant idea on a frosty morning of walking some three-quarters of a mile in his pajamas and slippers to a pond, where, breaking a thin film of ice, he took a short swim and then walked briskly home with small icicles clinging to the hairs on his body. That afternoon he had a chill and fever, and a pain in his left side, the lung on that side being the site of a long-existing tuberculosis which had remained uncured since 1894, twelve years previously. A small effusion at once developed and was left alone. After a stormy five weeks, with much fever, he recovered and never had another symptom of tuberculosis, and is alive and in good health for his age to-day.

[1] Visiting Physician, Detroit Tuberculosis Sanatorium, and the Leland After-Cure Farm.

One explanation that has been offered for such cures is that they result from the rest the lung gets from the compression exerted by the effusion. That will hardly do in elucidation of the phenomenon, as such cures are much more likely to follow a small rather than a large effusion. Why this should be so I do not know, but it has been true in my experience. The immunological and biochemical explanation is not much more satisfactory. Many times I have withdrawn 10, 20, even 50 cc. of clear transudate and injected it into the same and (Wassermann-negative) other patients, but never was I able to convince myself that any good resulted. So to-day we have no satisfactory explanation for the occasional sudden recoveries that follow pleurisy with effusion.

This really wonderful phenomenon deserves more attention from investigators than it has received, for in it somehow might be the key that would lay bare tuberculosis.

On account of the possibility of sudden cure I have always been careful not to disturb a small effusion. A large one is another matter, and must be handled differently. If it is not inconveniencing the patient unduly, leave it alone for a few weeks or months, so as to get the full effect of its mysterious and sometimes beneficent action, and then remove it and replace it with air if the condition of the other lung warrants continued compression. In cases in which it causes distress, either by its weight or interference with the heart and circulation, enough must, of course, be removed to afford relief.

A large effusion will seldom be resorbed as a small one often is. Its weight in itself is an inconvenience; it has a tendency to become purulent, and if the pus contains tubercle bacilli, we all know the answer,—the patient will die. I have witnessed but one recovery from tuberculous empyema, and in that case I maintained a constant flow of Carrel-Dakin solution in and out of the pleural cavity for six months, using a Murphy drip.

Not many patients would willingly lie in a puddle for that length of time, but this one did, and made a beautiful recovery, only to die of influenza during the 1918 epidemic. Left alone, a large effusion is often followed by gradual thickening of the pleura, and, too, its effect upon the compressed lung is not good,—just the reverse in fact from the effect of compression by means of air. It does not form a cushion like air, but rather a solid wall that is totally incompressible in itself.

Many years ago I had a patient who received artificial pneumothorax for five years for a severe lesion of the entire left lung with a good right

lung. She lived in another town, and, as time went on, neglected her fillings more and more, and returned at longer and longer intervals. The last two years I always removed clear fluid and replaced it with air. When, after being gone six months, she appeared for examination, I found the left pleural space filled with fluid. As it was late in the day I put her to bed in the infirmary, and told her I would remove the fluid in the morning. That evening, while she was eating her supper, she suddenly fell back dead. At the postmortem I found an interesting and unusual condition. The parietal pleura was about three-quarters of an inch thick. What was left of the pleural cavity was filled with clear fluid, in which floated what resembled a slightly used cake of white soap, composed of fibrin. What remained of the lung was a mass about the size of one's fist, with a dense half-inch shell on the outside and packed solid with caseous material on the inside, which under the microscope proved to contain innumerable tubercle bacilli. No pulmonic structure remained. The point is, of course, the effect upon the pleura of being bathed for years in transudate, with the vast thickening which follows long-continued immersion in serum. There was no pus or inflammatory action to explain the pleural change. Possibly, too, the cake of fibrin, knocking about in the pleural cavity for years, helped to cause thickening.

There are other lessons to be drawn from this particular case, such, for instance, as the possible effect upon a lung of long-continued compression, and the fact that such compression, even when very perfect and efficient in symptomatic relief, is not necessarily curative, but they are not germane to this paper and cannot be discussed here.

Some patients will state that they have never had any pleuritic pain, and yet when an attempt is made to induce pneumothorax the pleural space is found obliterated. From this it follows that a completely adhesive pleuritis may occur without pain. My own idea of this painless but still extensive and obliterative pleuritis is that it can only occur when the pleurisy begins at an apex in a portion of the lung relatively immobile and gradually extends downward, for a dry pleurisy in a mobile part of the lung will invariably cause pain. Many, in fact most, authorities maintain that the pleura, both parietal and visceral, is completely insensitive. I cannot believe this to be true. The visceral, yes; for one can puncture and burn the lung without pain, but the parietal is either very sensitive in itself or capable of reflecting various insults as pain. This is proved by the fact that not only does pleurisy often cause most

distressing pain, but one can tell, in anaesthetizing the chest-wall for artificial pneumothorax, when the needle strikes the pleura; for often the patient will flinch at that point. On the other hand, when burning off adhesions through a thoracoscope I never heard a patient complain of any special sensation. Anyway, the fact remains that pleurisy can be terribly painful, whatever may be the exact site of the pain.

Other patients will state that they have had much pleurisy, and yet the pleura will be found wholly or relatively free from adhesions when pneumothorax is induced. There is no safe deduction to be made from what the patient has to say, though, in general, it is safe to state that the more prominent pleuritic pain has been in the history the less likely will it be possible to obtain a satisfactory compression.

Pleuritic pain, as a complication of pulmonary tuberculosis, is the result of a tuberculosis involving the surface of the the lung, and, left to undergo its natural evolution, it frequently causes adhesions to the parietal pleura. Some writers have advanced the idea that natural pneumothorax would be much more common than it is if it were not for an adhesive pleuritis over a weakened area on the surface of the lung. This may be true, but when one recalls how seldom one encounters a natural pneumothorax during artificial pneumothorax it seems rather a weak argument for the usefulness of pleuritis. Also, it has been said that adhesive pleuritis limits the motion of the lung and aids in giving it rest, but certainly it cannot do this as efficiently as the gradual narrowing of the intercostal spaces which occurs in all long-standing tuberculosis, though the two probably proceed *pari passu*. In any event, it is a clumsy effort on nature's part to do something that can much better be accomplished by artificial fixation of the diseased lung.

In practice, even though it is a prominent symptom in but 6 to 8 per cent of all cases, I consider pleurisy an unmitigated nuisance, even granting that very occasionally a wet pleurisy will be followed by a mysterious "cure." First, it hurts, and, as said, it may be very painful indeed. It may be associated also with fever and cause increase of toxaemia. It may be the forerunner of an empyema which will destroy the patient, and, most important, it may result in either partial or complete obliteration of the pleural cavity, rendering a subsequent pneumothorax either out of the question or limiting its usefulness.

No one nowadays considers or studies a case of pulmonary tuberculosis without having in mind the possible application of artificial pneumothorax. We may need it as a strictly therapeutic measure, and again

it may be required for a time in a case in which it cannot be permanently applied,—in haemorrhage, for instance, in which it is in a class by itself as the only efficient means at our disposal for the control of this often serious complication.

It therefore seems reasonable to prevent, if possible, the occurrence of anything which might at the time or at any subsequent period interfere with the application of artificial pneumothorax, and the only mechanical impediment to pneumothorax is adhesive pleuritis causing either general adhesions or bands and strings, and sometimes even ropes. If such adhesions can be prevented, and one of the purposes of this paper is to show that they often may be, then we have not only conserved the possibility of a future pneumothorax but have perhaps saved the patient that dreadful ordeal of thoracoplasty, with its high immediate and ultimate mortality, and possibly, too, the lesser evil, phrenectomy.

Many years ago,—shortly after 1910,—I was asked to see one of my patients who had developed a severe pain in the side. I found her flushed with fever, sitting up in bed and making all the pressure she could exert over the painful spot, breathing as shallowly and as little as possible. This patient I had considered as a possible pneumothorax case, and, as I was about to send the nurse for the adhesive plaster (a poor and inefficient way of treating pleurisy, especially in a woman), it suddenly occurred to me, "Why not introduce some gas and separate the pleura?" This was promptly done with instantaneous relief of the pain.

Since then I have tried this method in 57 cases of pleurisy with and without pain, sometimes being guided only by the friction sound as to the existence of pleuritis. In every case I was able to introduce enough gas or air to stop both symptoms and signs if the latter were present. In some the artificial pneumothorax was continued indefinitely and in others just for the time being. I never saw it do any harm, and it never fails to stop the pain.

So simple a procedure must have been practised by others, and I therefore offer this paper, not with the idea of recommending something new, but as a testimonial to its efficiency.

THE ASSOCIATION OF TUBERCULOUS LYMPHADENITIS AND GENITOURINARY TUBERCULOSIS

F. J. LUSSMANN[1]

The fact that tuberculosis frequently affects certain groups of organs is well known. Sternberg (1), among others, has called attention to this, and has tried to bring this simultaneous susceptibility of certain organs to tuberculosis into vague relationship with the primary germ-layers from which the various organs are derived. A familiar prototype of simultaneous tuberculous disease of several organs is found in tuberculous involvement of a common triad, the lungs, the intestines, and the larynx, all of them derived from the entoderm. The bones, the lymph nodes and the serous membranes are also known to be frequently associated, while, though in rarer instances, tuberculosis of the ocular lens and of the skin (ectoderm) is not seldom reported to occur simultaneously.

The following is a report of the rather frequent occurrence of tuberculosis of the lymph nodes of the external-jugular-vein group, or of the intercostal lymph nodes and genitourinary system in patients afflicted usually with far-advanced pulmonary tuberculosis. As a rule, the diagnosis of genitourinary tuberculosis was in most of the cases previously established by routine clinical and laboratory examinations, and subsequent clinical examinations of the patients showed, with rather constant regularity, characteristic tuberculous involvement of the external-jugular-vein group of lymph nodes or the intercostal lymph nodes. The enlarged cervical lymph nodes presented a chain of two to six separate, round, pea-sized, hard, movable nodules that were slightly tender to pressure. They were either unilateral or bilateral, with no special relation to the side of the pulmonary involvement. A few of the cervical and especially of the intercostal lymph nodes underwent suppuration, and draining sinuses were formed as the result of incisions. No excision and microscopic examination of these nodes were made, but diagnosis was established on the above-described characteristics.

[1] Burlington, Wisconsin.

This report includes 23 adult patients with far-advanced and 2 with incipient pulmonary tuberculosis, all complicated by genitourinary tuberculosis. Renal and epididymal tuberculosis, as far as it was possible to make the distinction with safety, shared about equally in the entire number. On routine examination 16 of the patients showed the typical, above-described tuberculous cervical adenitis, with discharging sinuses following incision for abscess-formation in only two cases; 3 had intercostal sinuses following incision for suppurative tuberculous adenitis, and findings as to the lymphatic system were apparently negative in 6 patients. In control cases without genitourinary tuberculosis, this cervical or intercostal adenitis could only rarely be found. In a few cases the cervical or intercostal adenitis was followed by a tuberculous process in the genitourinary system within 4 to 12 months, and the presence of a tuberculous cervical or intercostal adenitis was eventually interpreted as a danger-signal of tuberculous involvement of the genitourinary system.

This coincidence of lymphatic and genitourinary tuberculosis represents a susceptibility to simultaneous or consecutive tuberculous disease of two physiologically entirely different groups of organs, which are derived from mesenchyme, or from mesothelium, both of which originally develop from mesoderm. This combination of simultaneous lymphatic and genitourinary tuberculosis is only second in frequency to the triad of pulmonary, intestinal and laryngeal tuberculosis. No effort has been made to explain this fact in the light of immunological standards, yet it may be mentioned that canalicular spread naturally does not come into consideration. But there is one practical conclusion to be drawn, which is that, if on examination of a tuberculous patient this lymphatic involvement is found; attention should automatically be directed to the genitourinary system, which, if it is not yet already diseased, may offer a most vulnerable point to tuberculous invasion, and all available preventive measures should be resorted to.

A short discussion of the probable way of infection of these particular lymph nodes and of the genitourinary system may not be amiss. It is generally, though not unanimously, conceded that the genitourinary system is infected *via* the blood. The external-jugular-vein group of lymph nodes is situated along the external jugular vein between the edges of the sternocleidomastoid and the trapezius muscles. It drains the scalp, external-ear region, and skin of the neck, but does not drain the upper respiratory or digestive tract or the apical parietal pleura.

The various groups of cervical lymph nodes communicate by collaterals, and this particular group might get infected through the lymph nodes of the internal-jugular or subclavian-vein system, which groups are, however, not readily accessible to the usual methods of examination. The afferent vessels of the intercostal lymph nodes drain directly the underlying part of the parietal pleura. However, the possibility of their infection by way of the blood must be kept in mind, which particularly offers a field of speculation as to the course of the disease, tuberculosis, taking its meaning in its widest sense.

Ranke (2) advocated the classification of tuberculosis into three stages, analogously to syphilis, the classification of which has been accepted universally. The primary stage or complex of tuberculosis, which nearly always is situated in the lungs, naturally antedates our referred manifestations in the lymphatic or other organic systems. The secondary stage or stage of generalization, which is characterized by pulmonary spread and the presence of tubercle bacilli in the blood, and especially in the lymphatic system, might be traced to these tuberculous lymph nodes; and tertiary tuberculosis, which is characterized by metastatic involvement of remote organs, may be referred to the tuberculous genitourinary system. This classification of Ranke's offers at least a chronological set of events and a complete picture of the infectious disease tuberculosis.

The above study leads to the practical conclusion that, if we find in patients with pulmonary tuberculosis, especially in the advanced stages, a tuberculous involvement of the external-jugular-vein group of lymph nodes or of the intercostal lymph nodes, special attention should be paid to the genitourinary system, as it is probably already tuberculously diseased or in danger of becoming so. This probability may prove of value to the general practitioner, to whom laboratory methods are not readily available. Preventive measures, more or less effective as they may be, may under circumstances be relatively early instituted.

From a theoretical and immunological standpoint this offers also a demonstration of the interesting fact of simultaneous or rather constantly successive tuberculous disease of two physiologically different organs, which possess however the embryonic relationship of descending from the same primary germ-layer, the mesoderm. These two groups of organs show a more constant simultaneous involvement by tuberculosis than does any other group of organs except that of the intestines and larynx.

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A STUDY OF 1000 CASES OF ADULT TUBERCULOSIS AND ITS BEARING ON DIAGNOSIS

I. C. MOLONY[1]

In the course of treating tuberculosis, patient by patient, and day by day, one tends to be unduly impressed by the case that is interesting and unusual and to form very definite and unjustifiedly biased judgment, due to strikingness rather than to frequency of occurrence. In view of this it seems important that one should, at stated intervals, review the experience of the past, and rearrange the various facts in the order of their frequency and importance, and thus by judicious selection replace acquired impressions with deductions from one's entire experience.

With this plan in view, four years ago the medical staff of the Fort Qu'Appelle Sanatorium, Saskatchewan, determined upon a certain form of history-taking, which would include the investigation of certain features and compel definite conclusions in regard to them. (See Plan of History.)

The histories of one thousand cases, together with the clinical records kept by the sanatorium during the course of treatment, have been the subject-matter for this thesis.

Before presenting the information regarding tuberculosis as observed among the cases studied it is necessary, for a fair interpretation, to tell something of the class of people included in the study.

One of the essential factors in this connection is racial resistance. It was found on compiling the statistics that the racial origins were varied. Just under 50 per cent (49.5) of this group were of British stock; just over 40 per cent (40.8) had origin in Continental Europe; 0.5 per cent had origin in Iceland and 0.7 per cent in Asia, and 3.7 per cent were North American Indians and half-breeds; while 4.9 per cent could not be classified for want of more definite information. An analysis of the data showed the percentages of very resistant races, such as Jews (less than 1 per cent), and that of very susceptible races, such as Indians and half-breeds (less than 4 per cent), to be so small that they had little effect upon

[1] Fort Qu'Appelle Sanatorium, Saskatchewan, Canada.

the resistance of the group as a whole; and in a general way one might say that the resistance represented that of the races of the British Isles and Continental Europe. (See table 1.)

In order to enable one to evaluate in some way the possible influence of early environment upon a group of tuberculosis cases it is necessary to give some idea of the place of birth of the individuals included in this group. A study of birth-places showed that 49.2 per cent were born in Canada, 19.3 per cent in United States of America, 12.6 per cent in the British Isles, 17.3 per cent in Continental Europe, 0.3 per cent in Asia, and 0.9 per cent in various other places. In general, just over 68 per cent

TABLE 1
Racial origins

	per cent		*per cent*
English	22.3	Polish	1.2
Scotch	15.5	Galician	0.4
Irish	11.0	Ruthenian	1.2
Welsh	0.7	Finnish	0.4
French	5.3	Luxemburger	0.1
German	8.3	Bohemian	0.2
Austrian	3.4	Greek	0.1
Hungarian	0.7	Czecho-Slovak	0.4
Belgian	0.1	Syrian	0.1
Norwegian	7.4	Orientals	0.6
Swedish	4.8	Doukabour	0.2
Russian	1.5	Indian	1.7
Dutch	1.2	Half-breed	2.0
Icelandic	0.5	Jewish	0.5
Ukrainian	1.9	Danish	0.6
Roumanian	0.8	Unclassified	4.9

were born in the rural communities of the North American continent, while just under 30 per cent were born under the environmental conditions of the British Isles and Continental Europe. The number from other places was so small that it would have no effect as far as resistance of this group is concerned. (See table 2.)

The fact that these individuals, who passed their childhood in widely different environments such as found in the British Isles, Scandinavia, France, Germany, Russia, United States and Canada where the death-rates from tuberculosis vary from 80 to 300 per 100,000, on being spread throughout a rural province such as Saskatchewan, immediately strike an average tuberculosis death-rate of 40 per 100,000, would indicate that

the environment of the province was probably a factor of importance. One should hasten to add that the process of natural selection operating during a period of colonization, when the fit and energetic tend to migrate, may be a factor of very great importance.

In order to make allowance for other factors involved we should bear in mind the effects of sex and marital relation. The number in each sex was nearly equal, 481 cases being males, and 519 females; and 187

TABLE 2

Place of birth

	per cent		per cent
Canada	49.2	Sweden	1.7
		Denmark	0.1
Quebec	3.4	Poland	0.7
Prince Edward Island	0.9	Austria	4.2
Saskatchewan	17.8	Hungary	0.8
Manitoba	6.2	Russia	3.1
New Brunswick	0.8	Iceland	0.1
Nova Scotia	2.8	Roumania	1.0
Ontario	16.6	Holland	0.2
Alberta	0.5	Ukrainia	0.8
British Columbia	0.1	Newfoundland	0.1
Province unknown	0.1	Serbia	0.2
		New Zealand	0.1
U. S. A.	19.3	Luxemburg	0.1
England	8.2	South Africa	0.1
Scotland	2.9	French East Indies	0.1
Ireland	1.4	Finland	0.2
Wales	0.1	Greece	0.1
France	0.5	South America	0.4
Germany	0.9	Burma	0.1
Belgium	0.1	China	0.1
Norway	2.6	Syria	0.1

of the men were married and 294 single. In the case of the women the proportions were reversed, 303 being married and 216 single.

The age of the patients studied ranged from 15 to 69 years. Chart 1 shows the age-incidence of morbidity per 100,000 in each five-year group, males and females being separated. The general features tend to coincide with the age-incidence of the young-adult type described by Brownlee in his *Epidemiology of Phthisis in Great Britain and Ireland, Report of Medical Research Committee, 1918.* The age of maximum susceptibility for each sex was determined by considering, year by year, the incidence between 20 and 29, as shown in chart 2. In the males the

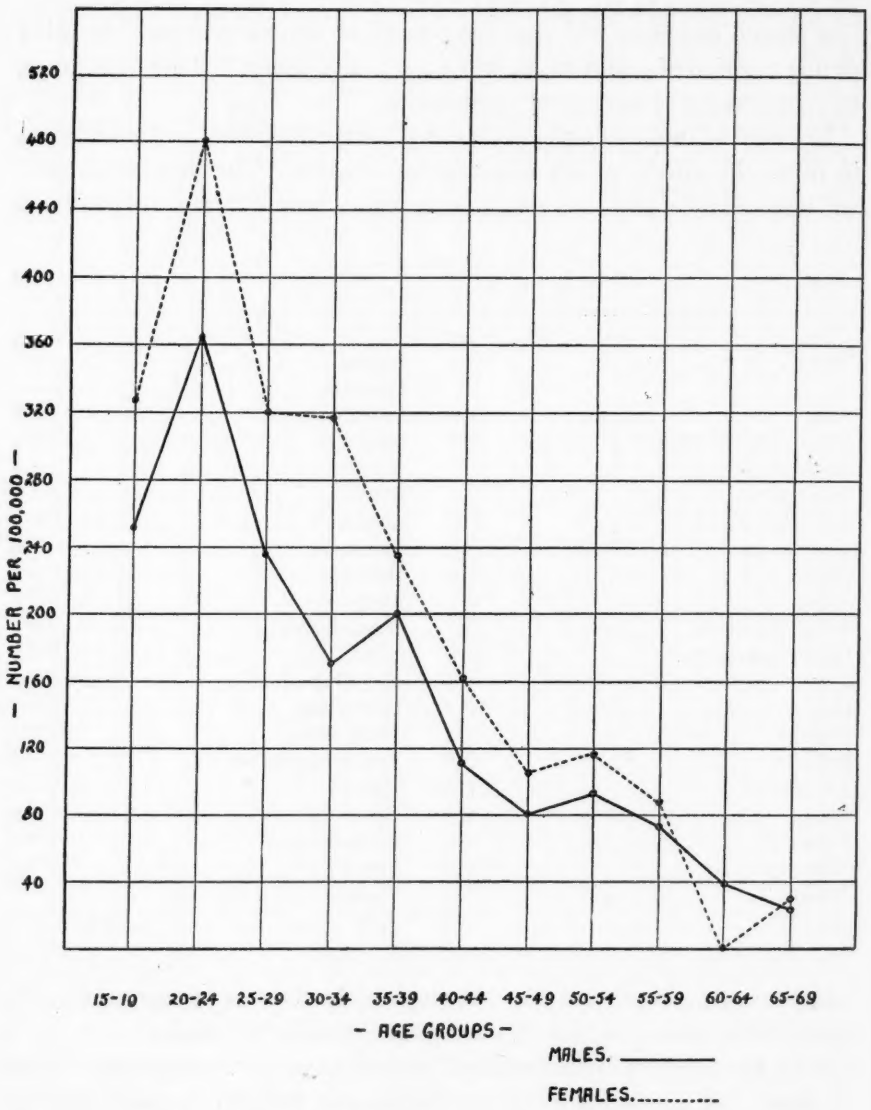

CHART 1. THE AGE-INCIDENCE OF MORBIDITY FROM TUBERCULOSIS PER 100,000 POPULATION BY SEX (CENSUS 1921)

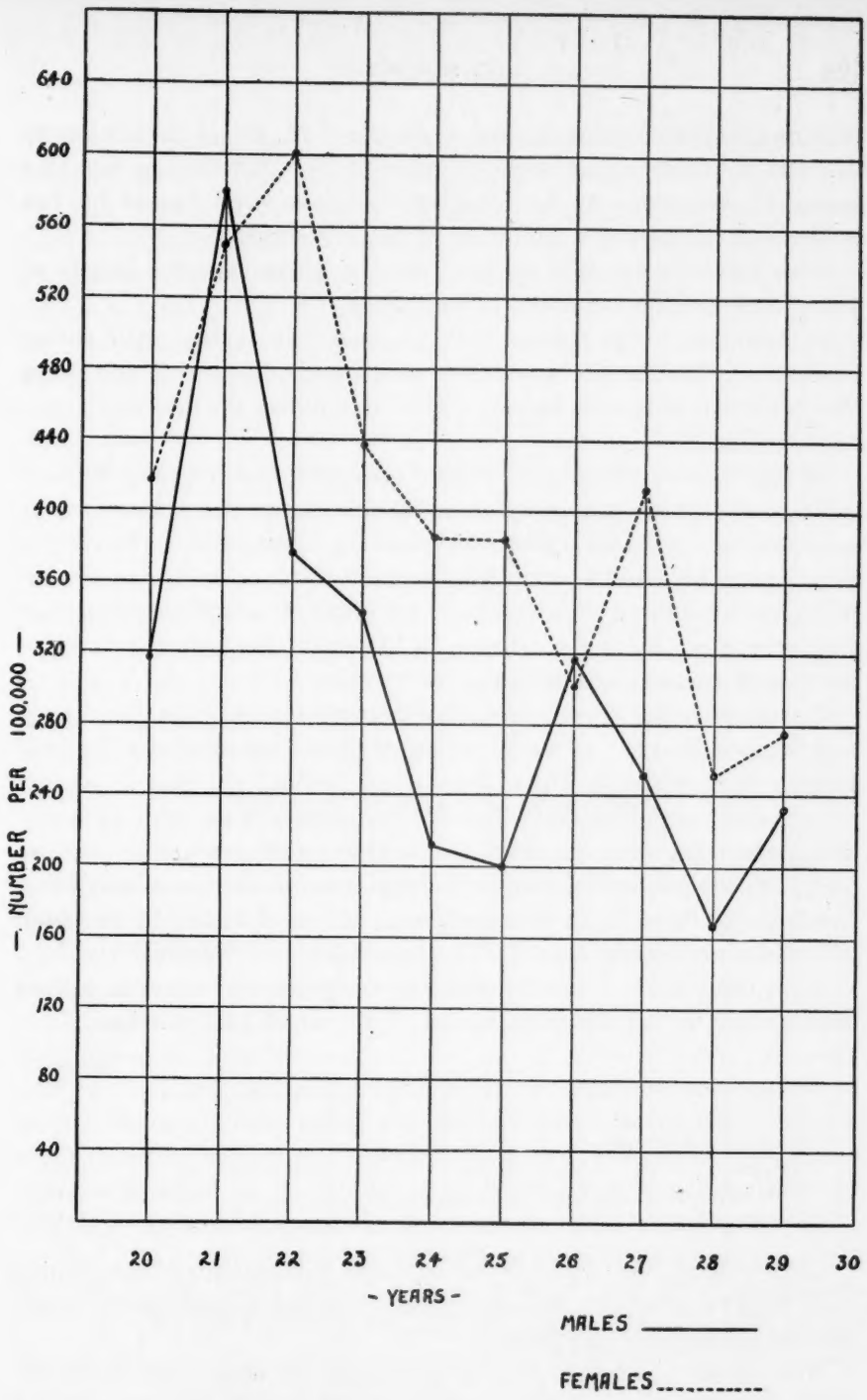

CHART 2. THE AGE-INCIDENCE PER 100,000 POPULATION YEAR BY YEAR, TO SHOW EXACT AGE OF MAXIMUM SUSCEPTIBILITY

peak of susceptibility was reached at the age of 21, and in the females at 22, with a secondary or slight increase at 27. Whether or not this secondary variation can be considered to have been caused by the influence of childbirth is a matter for further investigation.

From the foregoing it is evident that this group consisted largely of young and middle-aged adults of both sexes.

It should be noted further that to ensure this group representing conditions of civilian life no cases of men who had served in the Great War were included in this survey. This class, during the past four years, has been small.

As regards occupations, just under 50 per cent were following outdoor callings, and the indoor occupations listed were, on the whole, such as would be considered favorable in an industrial community. The various vocations which could be considered so unfavorable as to be a predisposing factor constituted even less than 1 per cent. It would seem therefore that occupation did not constitute an important factor in the development of tuberculosis in this group.

The cases studied were divided into the two major varieties, pulmonary and nonpulmonary. As would be expected in this age-group the pulmonary were greatly in the majority, namely, 90.2 per cent as against 9.8 per cent nonpulmonary. The number of cases in the nonpulmonary group was considered too small to justify detailed conclusions, but the varieties and frequency of adult nonpulmonary tuberculosis may be of interest. Of 98 cases 35 were peritoneal, 21 lymph nodes, 11 vertebral, 15 other osseoarticular lesions, 13 genitourinary, and 3 pleural.

Some conception of the chronicity of the pulmonary cases is derived from a study of the classification as to type, which was as follows:

	per cent
Chronic parenchymatous	93.9
Chronic fibroid	3.0
Acute parenchymatous	2.8
Pneumonic	0.1
Acute miliary	0.1
Chronic miliary	0.1

As is evident, the chronic type markedly predominated, constituting over 96 per cent of all pulmonary cases. This fact in itself speaks loudly for the resistance of this group.

The extent of disease and the proportion of open cases define the chief pathological coefficient upon which the study was based, and

modifies all deductions. Classification of cases was based on the standards laid down by the National Tuberculosis Association, and no case was included unless there were crepitations supported by definite parenchymatous mottling in the stereograph or by a positive sputum Just over 67 per cent were suffering from advanced disease, 20 per cent were in the moderately advanced stage, and just under 12 per cent were minimal at time of admission. The following table shows the distribution of the 902 pulmonary cases in detail:

	per cent		per cent
Group 1	11.9	Clinical	11.0
		Bacillary	0.9
Group 2	20.2	Clinical	15.6
		Bacillary	4.6
Group 3	67.4	Clinical	12.1
		Bacillary	55.3

Of the total pulmonary cases 61 per cent were bacillary, and in the case of 39 per cent no tubercle bacilli were found in the sputum with a moderate amount of laboratory effort.

RELATION OF ONSET TO ADMISSION

Throughout this study, which represents special investigation of all histories of tuberculous cases taken for a period of over three years, we have laid considerable stress on the onset of illness, hoping thereby to get a fuller knowledge of the first symptoms of the disease, and incidentally to determine the period elapsing between onset and breakdown.

The onset of symptoms of pulmonary tuberculosis is often indefinite and extremely difficult to determine, and even after careful histories were taken it was not always possible to determine the exact time of onset. When a disease comes on, as a rule, in a slow, insidious manner the person concerned is scarcely able to appreciate its presence until the time comes when he can no longer carry on his work and he actually falls sick, or some dramatic event occurs to bring the trouble to his notice. The term *Onset* in this study was taken to indicate the first occasion on which the patient was aware of symptoms of the disease. In many cases this onset was followed by a period of good health before the recurrence of illness which preceded the breakdown. For this reason very often a patient came under treatment long after the apparent onset of the disease.

TABLE 3

Showing condition of patients on admission in regard to extent of disease and presence of bacilli in the sputum at varying intervals from onset of disease

INTERVAL FROM ONSET TO ADMISSION	NUMBER OF CASES	PERCENTAGE OF CASES ADMITTED	PERCENTAGE OF CASES IN GROUP 1	PERCENTAGE OF GROUP 1 WITH BACILLI	PERCENTAGE OF GROUP 1 CLINICAL	PERCENTAGE OF CASES IN GROUP 2	PERCENTAGE OF GROUP 2 WITH BACILLI	PERCENTAGE OF GROUP 2 CLINICAL	PERCENTAGE OF CASES IN GROUP 3	PERCENTAGE OF GROUP 3 WITH BACILLI	PERCENTAGE OF GROUP 3 CLINICAL
Within 3 months	70	7.7	18.6	0	100.0	37.1	19.2	80.8	44.3	67.7	32.3
3 to 6 months	102	11.4	9.8	10.0	90.0	29.4	23.3	76.7	60.8	83.9	16.1
6 to 9 months	88	9.8	9.1	12.5	87.5	17.0	40.0	60.0	73.9	89.2	10.8
9 months to 1 year	45	4.9	11.1	0	100.0	17.8	25.0	75.0	71.1	78.1	21.9
Within 1 year	305	33.8									
1 to 2 years	165	18.3	13.3	9.0	91.0	14.6	16.7	83.3	72.1	88.2	11.8
2 to 3 years	86	9.5	11.7	10.0	90.0	24.4	23.8	76.2	63.9	83.6	16.4
3 to 4 years	77	8.5	7.8	0	100.0	24.7	21.0	79.0	67.5	80.8	19.2
4 to 5 years	35	3.9	20.0	14.3	85.4	14.2	20.0	80.0	65.7	86.9	13.1
5 to 6 years	34	3.8	14.7	20.0	80.0	8.8	33.3	66.7	76.5	92.3	7.7
6 to 7 years	37	4.1	24.3	0	100.0	16.2	0	100.0	59.5	59.1	40.9
7 to 8 years	25	2.8	8.0	0	100.0	8.0	50.0	50.0	84.0	71.4	28.6
8 to 9 years	18	2.0	5.6	100.0	0	11.1	0	100.0	83.3	60.0	40.0
9 to 10 years	14	1.5	7.2	0	100.0	21.4	33.3	66.7	71.4	90.0	10.0
Over 10 years	105	11.4	7.6	0	100.0	22.9	35.5	62.5	69.5	83.6	16.4

The time which elapsed between onset and admission is shown in detail as follows: Of the 902 pulmonary cases 7.7 per cent were admitted for treatment within three months of the apparent onset, as determined from the histories; 11.4 per cent between three and six months, 9.8 per cent between six and nine months, and 4.9 per cent between nine months and one year, giving a total of 33.8 per cent admitted within one year of onset; 18.3 per cent were admitted within the second year and 9.5 per cent within the third year. The numbers admitted during the succeeding years up to ten years from the onset have been given in yearly groups in table 3.

From a detailed study of this table it would appear in many cases that the disease had existed for a considerable period of time,—many months, if not indeed years,—before the first impressive symptom occurred. It would further appear that one would not be justified in bearing much prejudice concerning the extent of disease from knowledge of the length of time since the onset, as it has been shown that after the first nine months the proportion of cases in group 3 remained about the same, and was not increased by the lapse of many years. It was only in the first three months that the incipient and moderately advanced cases were in excess of the far advanced.

BREAKDOWN

A similar study was made with regard to breakdown with tuberculosis. The term *Breakdown*, as used here, denotes the time at which the individual could no longer carry on his ordinary activities, and had to rest in order to regain his balance of resistance and health. It was found that 31.8 per cent of the cases admitted had never broken down and were still carrying on their usual work until they came to the sanatorium, despite the fact that 57.8 per cent of these cases were already suffering from advanced disease. There were 19.6 per cent admitted within three months of breakdown, and here a larger number, 68.4 per cent, were suffering with advanced disease. A total of 45.1 per cent, or nearly half of the cases, were admitted within one year of breakdown. Table 4 gives this information in detail.

The most notable fact shown by these figures is that so large a proportion of persons will carry tuberculosis even to an advanced stage before breaking down, since of those whose disease was discovered and who were admitted to the sanatorium before they had actually broken down with tuberculosis just under 20 per cent were found to have minimal disease,

TABLE 4

Showing condition of patients on admission in regard to extent of disease and presence of bacilli in the sputum at varying intervals from breakdown with tuberculosis

INTERVAL FROM BREAKDOWN TO ADMISSION	NUMBER OF CASES	CASES ADMITTED	GROUP 1	PERCENTAGE OF GROUP 1 WITH BACILLI	PERCENTAGE OF GROUP 1 CLINICAL	GROUP 2	PERCENTAGE OF GROUP 2 WITH BACILLI	PERCENTAGE OF GROUP 2 CLINICAL	GROUP 3	PERCENTAGE OF GROUP 3 WITH BACILLI	PERCENTAGE OF GROUP 3 CLINICAL
		per cent	*per cent*			*per cent*			*per cent*		
No breakdown	287	31.8	19.2	7.3	92.7	23.0	27.3	72.7	57.8	79.5	20.5
Admitted under 3 months	177	19.6	8.5	0	100.0	23.1	24.4	75.6	68.4	78.5	21.5
Admitted 3 to 6 months	137	15.2	10.2	7.1	92.9	19.7	22.2	77.8	70.1	81.3	18.7
Admitted 6 to 9 months	58	6.4	3.5	0	100.0	13.8	25.0	75.0	82.7	85.4	14.6
Admitted 9 months to 1 year	36	3.9	13.9	60	40.0	19.4	14.3	85.7	66.7	91.7	8.3
Within 1 year	408	45.1									
1 to 2 years	73	8.1	13.7	0	100.0	15.1	9.1	80.9	71.2	86.5	13.5
2 to 3 years	28	3.1	3.6	0	100.0	21.4	33.3	66.7	75.0	80.9	19.1
3 to 4 years	17	1.9	5.8	0	100.0	11.8	0	100.0	82.4	78.6	21.4
4 to 5 years	15	1.6	13.3	0	100.0	20.0	33.3	66.7	66.7	90.0	10.0
5 to 6 years	12	1.4	0	0	0	8.3	0	100.0	91.7	100.0	0
Over 6 years	62	6.8	3.3	0	100.0	24.2	33.3	66.7	72.5	84.4	15.6

and just over 20 per cent moderately advanced disease, while nearly 60 per cent were already harboring extensive advanced disease.

In the case of those admitted within three months of breakdown the number in the advanced group had increased to nearly 70 per cent, and those in the minimal and moderately advanced stages had correspondingly decreased. After six months, however, there was practically no increase in the percentage of advanced cases found, even up to ten years from the time of the first breakdown. Again the maximum may be maintained by selection due to mortality. The foregoing emphasizes the fact that we shall never pick out early cases if we wait for people to fall sick before they are examined. Annual examination of well people is essential to the discovery of minimal cases. In a susceptible race, such as the North American Indians, many fall sick while still in the first stage, but among those of European descent very few fall sick until they have reached the advanced stages.

INTERVAL BETWEEN ONSET AND BREAKDOWN

The interval between first known symptoms of onset and the time of breakdown was determined as accurately as possible in each case. This varied widely, and comprised from a few weeks to many years. The average period in this group of cases was found to be two years and three months.

ENTRANCE COMPLAINTS

By making a careful study of the entrance complaints in the pulmonary cases considered, and summarizing the experience of several years, it was hoped to build up a better concept of the disease in the stage when its symptoms were first impressed upon the patient, so as to hand on to family physicians who meet these cases one by one a composite idea of the common complaints of a large group. The entrance complaints were taken down in each case as volunteered by the patient himself and were not elicited by any leading questions.

Since in many cases the patient complained of more than one symptom the number of complaints was far in excess of the actual number of patients. There were 1.9 per cent of the cases that volunteered no complaints at all on admission. These were examined as contact cases or for insurance purposes, or to determine their fitness for employment by the sanatorium, and in spite of the fact that they had no complaints a few had advanced disease, as shown by physical and X-ray examinations, and all had definite active tuberculosis.

Of the 902 pulmonary cases there were 130, or 14.3 per cent, that had no complaints referable to the chest. The various entrance complaints occurred in the following order of frequency: 1, cough (493); 2, weakness and fatigue (467); 3, pain in the chest (357); 4, abdominal disturbances, including anorexia, gastric pain and discomfort, constipation, and diarrhoea or any symptoms referable to the gastrointestinal tract (192); 5, dyspnoea (132); 6, loss of weight (109); 7, haemoptysis, including all cases from slight tinging of the sputum to haemorrhages of gross degree (102); 8, laryngitis (60); 9, sweating (48); 10, persistent colds (45); 11, headaches (23); 12, nervousness and sleeplessness (20), followed by a few vague symptoms, such as it seemed hardly worth while to tabulate.

It must be understood that these admission complaints were subject to the error of omission. Greater completeness could only have been procured by asking leading questions, which would have involved the greater error of redundancy due to suggestion. After taking the histories in many cases it was found that the patient had left out the more important complaints by not himself realizing their significance. A dramatic occurrence, such as a haemorrhage, seemed much more important to him than a sense of gradually increasing fatigue or loss of weight.

From these varied symptoms we learn how many complaints might and should lead us to think of the possibility of tuberculosis; and that however vague the symptoms, if no other cause is found, every endeavor should be made to rule out the possibility of the disease. Though the number of pulmonary cases that had no complaints referable to the chest was small (14.3 per cent) it must be remembered that failure to complain of these symptoms does not rule out pulmonary tuberculosis. On the other hand it is evident that we must not ignore the patient's own complaint, as in 85.7 per cent of our cases it drew attention to the particular organ involved.

SYMPTOMS UNDER TREATMENT

The symptoms under treatment cover different periods, according to the length of time the patients remained in the sanatorium, varying from about three months to three years, with an average of about ten months. These were more complete and reliable than the complaints on admission, as they were in every case interpreted by a physician and occurred in the case of people already known to be sick with tuberculosis. The frequency of occurrence of symptoms in the 902 pulmonary cases was as follows:

Frequency of occurrence of symptoms while under treatment

Cough	770	Nervousness	39
Pleurisy	489	Pain in neck	28
Headache	428	Fatigue	26
Sore throat	273	Renal symptoms	26
Abdominal pain	238	Palpitation	25
Haemoptysis	238	Melaena	22
Emesis	217	Oedema	22
Nausea	202	Ischiorectal pain	13
Anorexia	168	Swollen lymph nodes	12
Diarrhoea	164	Discharging sinuses	9
Huskiness	137	Abdominal distention	6
Chills and sweating	112	Ophthalmalgia	4
Backache	93	Meningeal irritation	3
Epistaxis	89	Asthmatic attacks	2
Neuralgia and arthritic pains	77	Hiccough	2
Sleeplessness	73	Depression	1
Earache	61	Painful testes	1
Dyspnoea	39	Purpuric rash	1

It will be observed that a number of symptoms frequently complained of on admission such as dyspnoea, fatigue and nervousness, were rarely noticed by the patients after being put at rest in the institution. For this reason both admission and treatment complaints should be considered together in order to embrace the complete symptom-complex of active disease.

Although many cases may present a text-book picture of tuberculosis, there are many others that will vary markedly from this picture and present other symptoms such as the clinician might miss without a knowledge of many cases.

"RESISTANCE" OF FAMILY STOCK

From the family histories of a thousand cases a study was made of the apparent resistance of the family tree in relation to tuberculosis. It must be remembered that the data given by the patients were in accordance with the best of their knowledge, and there undoubtedly were some in whose families there were cases of tuberculosis unknown to them. Therefore these data err largely on the side of omission.

The resistance of the family tree was considered to be represented by the number of cases of tuberculosis in the patient's family, including children, brothers, sisters, parents, grandparents and collaterals, and was divided into six different groups.

1: Excellent: Showing no history of any tuberculosis in any of the groups mentioned.
2: Indefinite: Negative, but inadequate information as to family history.
3: Good: No case of tuberculosis in a nearer relative than one grandparent or one collateral relative.
4: Fair: One case of tuberculosis in immediate family alone, that is, children, brothers, sisters or parents, or one in family and one in collaterals, or more than one in collaterals alone.
5: Poor: One in family and more than one in collaterals, or two in family.
6: Bad: Three or more in immediate family.

The importance of this study was to bring out the susceptibility of the group of patients on which our experience has been based. Studied in this way the percentages in the different groups were as follows:

Excellent	55.9	Fair	19.5
Indefinite	8.2	Poor	8.7
Good	4.2	Bad	3.5

The group *Excellent* showed a very high percentage, indicating over 55 per cent of the patients as having had no family history of tuberculosis. The number of patients with a really bad family history was found to be as low as 3.5 per cent, while *Poor* and *Bad* together constituted 12.2 per cent.

FAMILY DISEASE

The investigation of family disease in one thousand cases shows not only the resistance but also indicates the amount of close contact encountered in the group studied, and the possibility of massive infection in adults; and may almost be described as "house disease."

MacCorison and Burns (*Boston M. & S. J., 1913*) discuss the rôle of "Family Clusters" in the prevalence of pulmonary tuberculosis. They conclude that "The domiciliary distribution of tuberculosis may be due wholly or in part to the establishment of foci of infection following carelessness of individuals, usually adult, open cases of disease. The swiftest channels of spread of disease and furtherance of its activity are through the family lines."

In considering family disease, that is, the actual incidence of tuberculosis in the immediate family of the patient, not including grandparents and collaterals, the information can be considered as fairly accurate. Cases of tuberculosis in brothers, sisters and parents are usually remem-

bered by the patient. In the case of patients who could give no history of any tuberculosis in their families, family disease in this latter restricted interpretation, was considered to be negative, and the positive cases were divided up into separate headings of one in family, two in family, three or more in family; and again there were a certain number with negative but inadequate information on this subject and they were classified as indefinite.

These were as follows:

	per cent		per cent
Negative	61.9		
Indefinite	7.9		
Positive	30.2	one in family	19.1
		two in family	7.9
		three or more in family	3.2

According to a survey made at Saranac Lake (AMERICAN REVIEW OF TUBERCULOSIS, June, 1918) there were 61 per cent of negative family histories obtained. Both this and our present study indicate that the resistance of the family did not entirely protect the individual and the absence of a positive family history justifies no conclusion regarding freedom from disease.

CONJUGAL TUBERCULOSIS

In order to obtain information on the incidence of consort tuberculosis a study was made of the married patients. This also throws some light on the general resistance to the disease but more particularly on the importance of massive infection among adults. The number of the married was very nearly half the total cases, namely 490. Of these 490, some of whom were men and some women, there were 29 whose consorts were now or had been suffering from tuberculosis. Some gave a history of husband or wife dying of the disease, some had taken treatment for it elsewhere, and in some cases both husband and wife had been treated in this sanatorium. This showed the incidence of tuberculosis in the consort to be at the rate of 5.1 per cent of the married cases, or just over twice the incidence found among 17,436 adult males, between the ages of 18 and 45, called up from Saskatchewan for service under the military-service act in Canada in 1918. It should be borne in mind, however, that there was a great difference in the method and thoroughness of the examination, as in the cases studied here careful histories were taken and the X-ray used as routine.

A study was made by S. Rowland (*Lancet, December 3, 1924*) on conjugal tuberculosis in Northampton, England, in the ten-year period, 1911 to 1920 inclusive. The author found that in that decennium one partner infected the other in only 2.7 per cent of the cases, an incidence that varied little from the generally accepted figures for the clinical-tuberculosis rate for the general population. In Saskatchewan the incidence of infection of consorts was more than doubled, showing that although the rate of incidence is higher between husband and wife than that found in general, it is not so high as one might expect if adult massive infection were of very great importance, as husband and wife are more exposed to each other than are any other two people in the community.

TABLE 5

Frequency of exposure and interval between known exposure and onset of disease in 1000 cases

Known positive exposures	226
Onset within 1 year of exposure	16
Onset 1 to 2 years from exposure	19
Onset 2 to 3 years from exposure	9
Onset 3 to 4 years from exposure	17
Onset 4 to 5 years from exposure	6
Onset 5 to 6 years from exposure	13
Onset 6 to 7 years from exposure	11
Onset 7 to 8 years from exposure	5
Onset 8 to 9 years from exposure	9
Onset 9 to 10 years from exposure	7
Onset over 10 years or indefinite time from exposure	114

IMPORTANCE OF EXPOSURE

The reason for studying exposure was to determine, if possible, the importance of previous known exposure in causing breakdown in adult life.

Of the 1000 cases reviewed there were histories of only 226 positive exposures, or just over 22 per cent. Of these positive exposures there were 114 cases in which the onset was over ten years or an indefinite time after the known exposure. Since 78 per cent acquired the infection without known exposure it is reasonable to conclude that the importance of exposure and massive infection in adult cases should not be overemphasized in diagnosis. There were 112, or 11.2 per cent, of cases with a positive exposure and an onset of disease within a reasonable time of exposure, that is, ten years or less. These were divided into

yearly groups between exposure and onset, and in no year did the number reach as high as 2 per cent, the highest being 1.9 per cent between one and two years from exposure (see table 5).

In a group of 3083 cases studied by Lyle Cummins there were 39.4 per cent that had a positive history of exposure (*Tubercle, May, 1926*). The lower incidence in this province is possibly due to our lower mortality rate.

It would appear from our study that the majority pick up disease without, to their knowledge, being exposed, and we should not overrate the importance of known exposure among adults in an immunized community.

Lest there be misunderstanding through failure to bear in mind the effect of age it should be stated that our experience in regard to effect of known contact in the case of children of these people, living in the same homes, though too limited to justify a definite conclusion, is quite the reverse of that with adults and shows a marked increase of disease when there is known exposure.

CONCLUSION

In conclusion, it should be stressed that the people included in this study were of British and diverse European stock, modified by certain influences of selection associated with migration. The class of patients previously detailed, of which 10 per cent were hopeless on admission, were those who had been referred by family physicians for treatment to an institution admitting all types. Still there was known to be some selection by both parties. The conditions on the whole were influenced by two principal factors, namely, colonization, and sparsity of settlement in an agricultural district. The clinical type here described would seem to be fairly representative of that obtaining in the geographical area referred to, but it is probable that the deductions,—the result of group experience,—may be somewhat modified by time and place.

SUMMARY

1. After nine months had elapsed from the onset of the disease the proportion of advanced cases remained about the same, and was not appreciably increased from year to year.

2. Of the 287 whose disease was discovered and who were able to carry on their occupation and usual activities up to admission, just under 20

per cent were found to have minimal, just over 20 per cent moderately advanced, and nearly 60 per cent advanced disease. It seems evident that a large proportion of people have such a high tolerance for tuberculosis that they will carry it even to an advanced stage before breaking down.

3. The average interval between the first known symptoms of onset and the time of breakdown in this group was found to be 2 years and 3 months.

4. The number of pulmonary cases that volunteered no complaints referable to the chest on admission (14.3 per cent) was large enough to emphasize the fact that failure to complain of chest symptoms does not rule out pulmonary tuberculosis.

5. By their complaints of symptoms referable to the chest, 85.7 per cent of pulmonary cases drew attention to the particular organ involved. It is evident that the diagnostician should listen attentively to the patient's complaints.

6. Abdominal disturbances constituted the fourth most common complaint on admission, and five out of the ten most frequent symptoms under treatment in the pulmonary cases. Symptoms below the diaphragm must never be dissociated from this nominally lung disease, for, while sometimes due to abdominal tuberculosis, they are in many cases due to the toxaemia of the disease.

7. Three of the twelve important complaints on admission were constitutional. In some of these cases the symptoms were merely those of focal infection, which on examination was discovered to be in the lungs and to be tuberculous.

8. The most prominent and reliable symptom was pain in the chest, which, when observed under treatment, proved to be pleurisy. This was the third most frequent complaint on admission and the second most frequent under treatment. It occurred twice as frequently as haemorrhage and blood-spitting, and four times as frequently as chills and sweating.

9. Over 60 per cent had no definite history of tuberculosis in the immediate family, indicating that the resistance of the family did not entirely protect the individual, and that the absence of positive history justified no conclusion regarding freedom from disease.

10. The incidence of tuberculosis among the consorts was twice that of the average population in the same area. This is an important group to search for active cases; nevertheless the incidence is so low (5.1 per cent) that the increased frequency should be given little consideration in diagnosis.

11. Since 78 per cent acquired the infection without known exposure the importance of this event in adult life should not be overemphasized in doubtful cases, and absence of exposure should not be considered as excluding tuberculosis.

12. By moderate laboratory effort tubercle bacilli were found in only 60.8 per cent of 902 pulmonary cases. Failure to find bacilli in the sputum should not be allowed to rule out tuberculosis.

Plan of History Taking

1. *Entrance Complaint:* By complaint is meant the symptoms on date of admission. Only the complaints volunteered by patient are to be recorded under this heading, and it is not to be a summary of symptoms elicited by leading questions.

2. *Present Illness:* Starting from when the patient was last well state in detail the onset and development of symptoms in order of occurrence with full details and dates. Symptoms elicited by leading questions should be included under this heading.

3. *Other Systems:* Investigate cardiac, genitourinary, gastrointestinal, respiratory, circulatory, nervous and endocrine systems.

4. *Past Illnesses:* Record health history apart from present illness, giving full details and dates. This is to include onset, symptoms, and course of the disease, and sequellae, and a separate statement as to whether there was a complete recovery of health in each case. Investigate especially focal infections, tonsils, teeth, sinuses, gall-bladder, appendix, urethra, etc.

5. *Family History:* Make a statement regarding father, mother, brothers, sisters, consort, children, grandparents and collaterals as to whether they are alive and well, or dead, also giving ages.

6. *Personal History:* Investigate carefully racial descent on father's and mother's side, place in family, place of birth, childhood, school days, hours of occupation, living conditions, recreations, and habits, stating whether the patient is ambitious, inclined to worry, and also giving a history of marital and menstrual conditions.

7. *History Supplement:* (To be made from history and proof given for conclusions reached.)

   (1) *Exposure to Tuberculosis:* State infection in family or associates, giving details and dates of exposure, with age of patient at time of exposure.

   (2) *Onset:* Give date, manner and details of disease or condition associated with onset.

   (3) *Breakdown:* Give details of recent and previous breakdown (if any) with date and determined cause.

(4) *Sputum:* If examined, state, where, when and how often.
(5) *T. B. Tips:* State previous and early "hunches" or indications of disease, which might have aroused suspicion.
(6) *Recommendation:* State on whose advice patient came to the sanatorium.
(7) *General Appearance:* Give enough details to give picture of patient.
(8) *Complaints:* List complaints or circumstances, however remote, which led patient to first seek advice regarding present trouble.

A STUDY OF THE TUBERCULOUS LESIONS IN THE LUNG OF A NEGRO CHILD NINE WEEKS OLD[1,2]

II. A TUBERCULOUS LYMPH NODE SITUATED IN THE INCISURA INTERLOBARIS WITH ITS AFFERENT AND EFFERENT LYMPHATICS

WILLIAM SNOW MILLER

When a tuberculous lesion has established itself in the human lung, it rarely remains localized at the point where it first developed, but extends to other parts of the lung through dissemination of the tubercle bacilli. This dissemination may take place through the lymphatic system, through the blood-vascular system, by peripheral extension of the original lesion, or through the bronchi.

The present communication is a continuation of the study of the lung described in the October, 1928, issue of the AMERICAN REVIEW OF TUBERCULOSIS. The course of the lymphatic through which a small lymph node became infected, and the further course of the lymphatics, after they have passed through the lymph node carrying the infection to one of the larger lymph nodes situated at the hilum of the lung, will be described.

In figure 1 the topography of the lymph node (indicated by the arrow) is shown. It is situated in the pleura of the left upper lobe, which forms one side of the *incisura interlobaris*, approximately 4 mm. from one of the large lymph nodes at the hilum of the lung. From the left side of the node a broad connective-tissue septum extends into the upper lobe; this marks out a triangular area of pulmonary tissue,—a portion of a secondary lobule. A narrow septum joins the broader septum near the centre of its left arm; this also marks out part of a secondary lobule. At the junction of the two septa three miliary tubercles can be seen; however, they are neither directly nor indirectly connected with the lymph node which is situated directly above them. The lymph node measures 2.2 mm. from side to side, 2.4 mm. from above downward, and

[1] From the College of Medicine, University of Wisconsin, Madison, Wisconsin.

[2] Aided by a grant from the National Tuberculosis Association.

1.36 mm. in thickness, the measurements being taken through the greatest diameters.

On the extreme margin of the triangular area situated at the right of the lymph node there can be seen in figure 1 two miliary tubercles. There is a third member of the group, figure 2, which is situated in the connective-tissue septum at the point where it arches upward to join

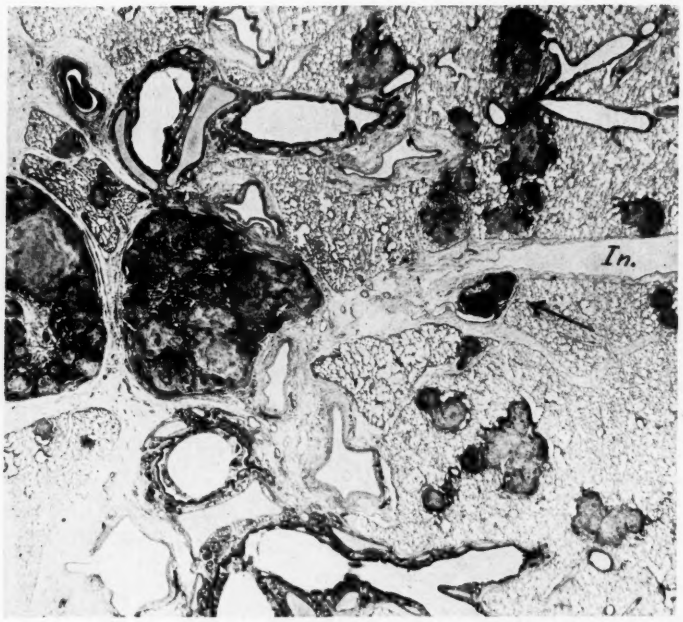

FIG. 1. General topography of the lymph node that was reconstructed. The arrow points to the node. It is situated in that part of the pleura of the left upper lobe which forms one side of the *incisura interlobaris* (*In.*). The large lymph nodes on the left of the photomicrograph are hilum nodes which show extensive involvement. One of the efferent lymph-vessels can be seen leaving the node. Its ultimate connection with the large lymph node nearest it can be traced in the series, though it does not appear in the reconstruction. The upper lobe is below, the lower lobe is above the incisura. ×5.

the pleura. This third tubercle apparently had its origin by a peripheral extension of the deeper of the two tubercles in the secondary lobule into the connective-tissue septum. It is from this tubercle, situated in the septum, that the infection can be traced to the small lymph node shown in figure 1.

Only a small portion of the lymphatic which transported the infection (bacilli) from this focus to the lymph node appears in this section. The

lymphatics which are present in the pleura, figure 2, form no part of the direct line of communication between the focus of infection and the lymph node, although they do enter into the lymphatic network shown in figures 11 and 12.

The course through the connective-tissue septum of the lymphatic which carried the bacilli from the tubercle shown in figure 2, its junction

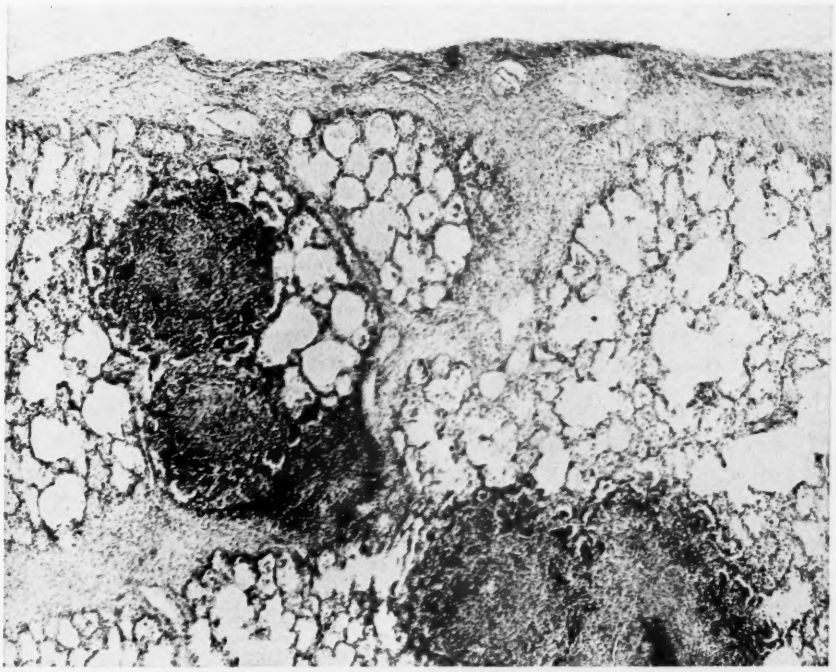

FIG. 2. The focus from which the infection was traced to the lymph node. Note the wide connective-tissue septum and the tubercle which is situated within it at the point where it arches upward to join the pleura. Above the tubercle, and also at its right, sections of the radicles which unite to form the larger trunk (white in figures 11 and 12) can be seen. Two of the lymphatics in the pleura contain a valve; in the smaller one the valve is cut transversely; in the larger vessel it is cut longitudinally. These lymphatics form part of the reconstruction, but they are not part of the direct line of infection. ×35.

with a pleural lymphatic, and the valve placed at its entrance into the pleural lymphatic, are shown in figure 3. The valve points (opens) toward the pleura and indicates the direction of the lymph-flow. No valves are present throughout the course of the lymphatic in the connective-tissue septum. The distance from the tubercle in the septum to the junction of the lymphatics in the pleura is approximately one

millimetre. The small lymphatics on the left of figure 3 do not join the larger vessels, but belong to a different set.

If the lymphatic be followed toward its entrance into the lymph node, it will be found that there are numerous valves along its course. One of these valves is shown in figure 4, and, like all the others, it opens toward the lymph node. The entrance of the lymphatic into the lymph node is shown in figure 5 and in figure 11 (white vessel).

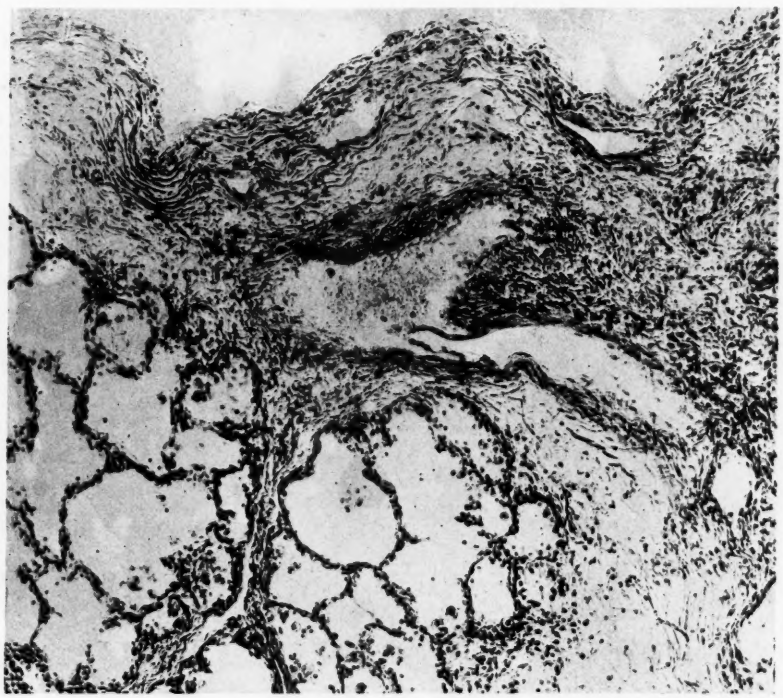

FIG. 3. Section of the connective-tissue septum, the lymphatic which carried the bacilli to the lymph node, and the valve at its junction with the pleural lymphatic. ×100.

The remaining afferent lymphatics unite to form two distinct systems, one of which enters the lymph node on its pulmonary side, while the other enters the node on its pleural side. Both of these systems are colored yellow in figures 11 and 12, while the lymphatic which carried the infection to the lymph node is colored white.[3]

Indicative of its internal structure, the lymph node can be divided

[3]For convenience of description the lymphatics are classified as "white" and "yellow."

externally into two portions, one of which is colored pink, the other yellow in figures 11 and 12. The lymphatic which brought the bacilli to the node enters the former, while the other two systems enter the latter.

Following the course of the lymphatic bringing the bacilli to the node it was found that, after its entrance into the node, all of the sinuses connected with it had been obliterated by the tuberculous process. Figure 5 is taken from a section near the centre of the area colored pink in figures 11 and 12. Nearly the whole of the section is involved in the

FIG. 4. One of the valves in the lymphatic after its entrance into the pleura. The valve opens toward the node and shows the direction of the lymph flow. ×100.

tuberculous process. A branch of the bronchial artery occupies a portion of the trabecula which separates the tuberculous from the nontuberculous area. Portions of two germ-centres can be seen in the nontuberculous area; they form the upper part of that portion of the node (yellow) which is situated between the tuberculous (pink) part of the node and the large lymphatic which runs throughout its entire course outside of the lymph node, figures 11 and 12. The lymph sinuses surrounding these germ-centres have no connection with the lymphatic which brought the bacilli

to the node. The entire area of that part of the node situated above the level of figure 5 is tuberculous. No caseation is present.

Figure 6 is from a section 280 micra below figure 5. The tubercles have become more circumscribed; both contain numerous giant cells and the one at the left shows a slight amount of caseation. Although

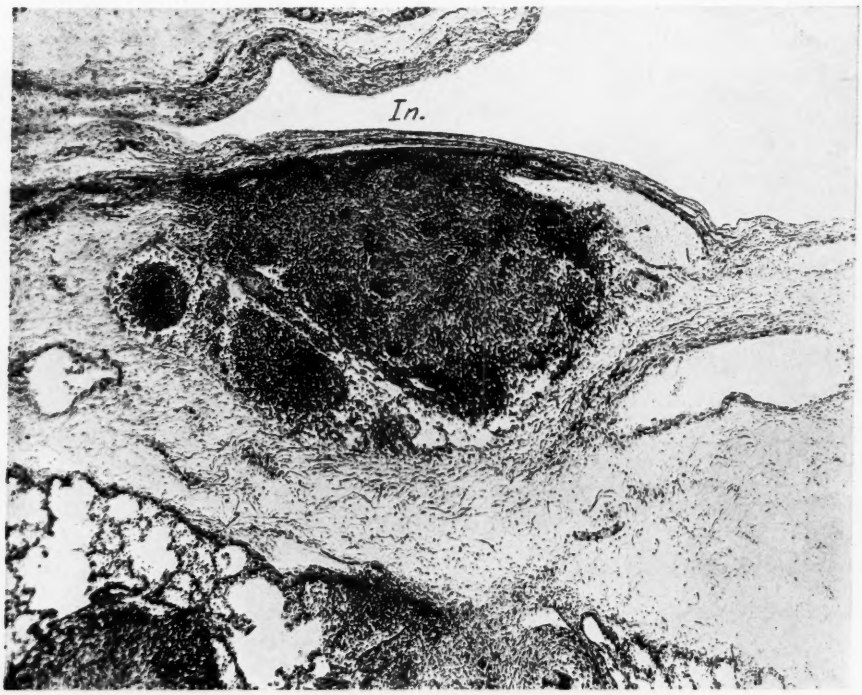

FIG. 5. Section through the lymph node, showing the lymphatic through which the bacilli entered the node. The large lymphatic on the right of the node, and below the one bringing the bacilli, is an oblique section of the lymphatic (yellow) which is passing obliquely along the right side of the node in figure 12. The greater part of the node is tuberculous. A branch of the bronchial artery occupies a portion of the trabecula which divides the tuberculous from the nontuberculous (hyperplastic) part of the node. On the left, outside of the node, is a section of the lymphatic which runs entirely outside in the node; best seen in figure 12. Note the valve and that it points (opens) away from the node. *In.:* Incisura interlobaris. ×40.

the tubercles are in juxtaposition to wide-open lymph sinuses, the sinuses are free from exudate. No communication can be traced between the sinuses and the lymphatic which enters the node in figure 5; they are, however, in communication with the lymphatic which enters the node on its pulmonary side.

A new factor which made its first appearance in figure 5,—hyperplasia of the lymphoid tissue,—now begins to assume a prominent place in the sections. The lymph sinuses which are in immediate contact with these areas contain numerous lymphocytes and large mononuclear leucocytes; some of the latter contain ingested material (phagocytes).

The tubercles have entirely disappeared in figure 7, and the entire section shows intense hyperplasia of the lymphoid tissue. The interesting features of figure 7 are connected with the lymphatics and the lymph sinuses. The section cuts through the plane at which two afferent lymphatics (yellow in figures 11 and 12) enter the lymph node. Both

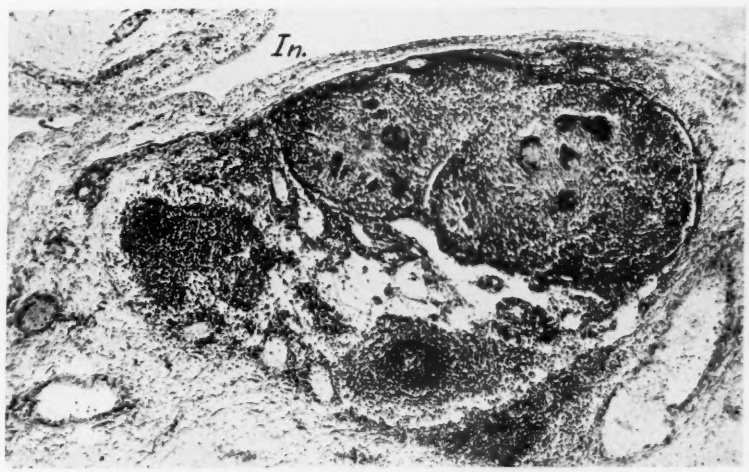

FIG. 6. Section through the lower part of the tuberculous area of the node. The large lymphatic on the right is a continuation of the one occupying a corresponding position in fig. 5. Further description is contained in the text. *In.:* Incisura interlobaris. ×40.

of these afferent lymphatics are formed from an extensive network of pleural lymphatics, whose radicles are in connection with tubercles situated in the parenchyma of the lung with offsets into the septa similar to the one shown in figure 2. They differ from the lymphatic which enters the upper pole of the node in that, *although they traverse active tuberculous processes, they do not give origin to tubercles within the lymph node.*

The trunk which enters the node on its pleural side gives origin to a sinus which can be traced along the entire pleural surface of the node. As it arches around the germ-centre on the left of the figure, a dilated

crescent forms a prominent feature. Special attention is called to the rounded projection which forms the highest point of this crescent; for from it arises that short lymphatic which passes perpendicularly along the pleural surface of the node and eventually opens, through a valve, into the efferent trunk which emerges from the bottom of the node on its pleural side, figures 9 and 11. This is the most unique lymphatic I have found.

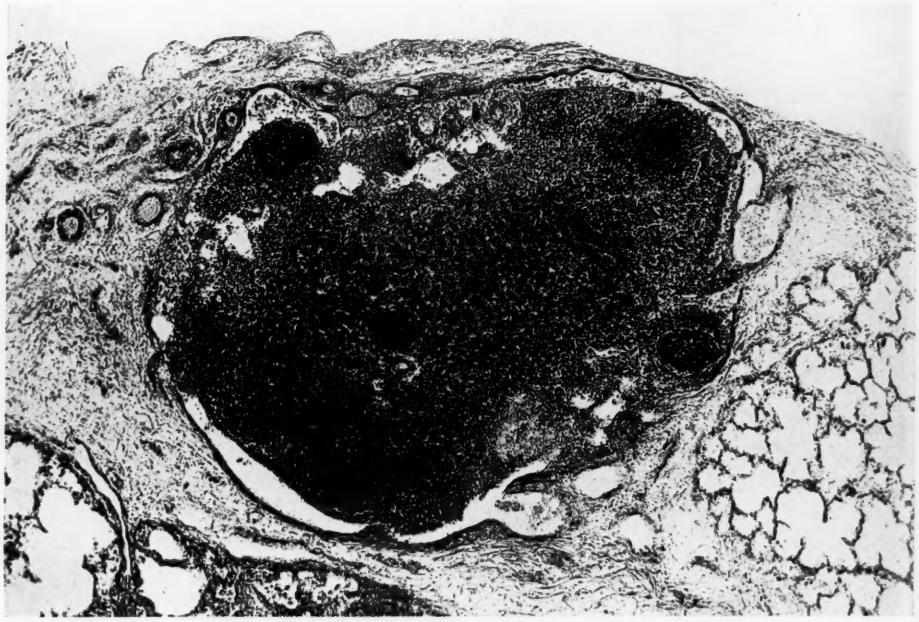

FIG. 7. The tubercles have disappeared and hyperplasia of the lymphoid tissue occupies the entire section. The entrance of the afferent lymphatics is shown on the upper and lower right of the section. The crescent-shaped sinus mentioned in the text can be seen arching around the germ centre in the upper left. ×40.

A number of irregular sinuses open out from the one that runs along the pleural side of the node and extend a short distance into the hyperplastic area of the node; their ultimate connection will be considered in the description of figure 8.

The afferent trunk which enters the node on its pulmonary side opens into two sinuses, figure 7. One of these passes toward the pleura and eventually connects with the sinus which runs along the pleural side of the node, figure 8; the other passes along the pulmonary side of the node and is much the larger of the two.

The hyperplasia, which increased from its first appearance in figure 5 until it completely filled the section in figure 7, presents the same character in figure 8, and maintains this through the remaining sections of the node.

By following the course of the sinuses around the periphery of the node in figures 7 and 8, it will be found that they completely encircle the node and eventually unite to form the large efferent lymphatic which

FIG. 8. The hyperplasia present in figure 7 is continued in this section and through the remainder of the node. The sinus, which forms the "the wide open bypath" mentioned in the text, can be seen on the pulmonary side of the node; also its direct continuation into an efferent lymphatic. Note the valve in the efferent vessel and that it points (opens) away from the node. ×40.

leaves the node on the left in figure 8 (orange in figure 12). The sinus on the pulmonary side of the node deserves special notice, for it forms a wide-open bypath through the node and at the same time the major part of the efferent lymphatic in figure 8.

The second efferent lymphatic, figure 9, is situated on the pleural side of the node, figure 11, and is somewhat smaller than the one on the pulmonary side. It is formed by the union of the irregularly shaped sinuses, which are seen on the pleural side of the node in figures 7 and 8,

and the lymphatic which runs perpendicularly along the pleural surface of the node. Since this lymphatic is situated outside of the node and takes part in the formation of the larger efferent lymphatic, it must also be considered an efferent vessel, and is accordingly colored orange in figure 11.

The efferent lymphatics, after a long and tortuous course, unite just before they become connected with the large hilum lymph node which is

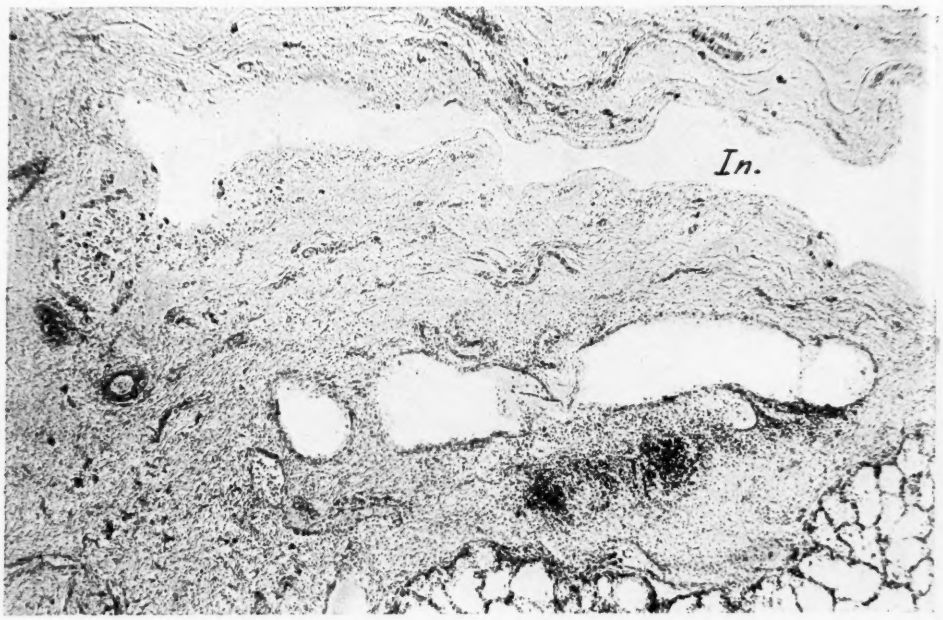

FIG. 9. The continuation of the sinuses seen in the hyperplastic area of figures 7 and 8 unites with the lymphatic which runs perpendicularly along the surface of the node and forms the efferent lymphatic which leaves the pleural side of the node. The two clusters of cells on the pulmonary side of the efferent lymphatic are the final sections of two germ-centres and also the last section of the lymph node. ×40.

situated nearest the *incisura*. The efferent lymphatic which leaves the node on its pleural side is, throughout its course, practically free from any contents; on the other hand, the large efferent lymphatic, which continues the wide-open bypath on the pulmonary side of the node, is filled with exudate, figure 10. Both efferent vessels contain valves; but they are more numerous in the one that leaves the pulmonary side of the node, figure 10.

The lymphatic which joins the efferent lymphatic leaving the node

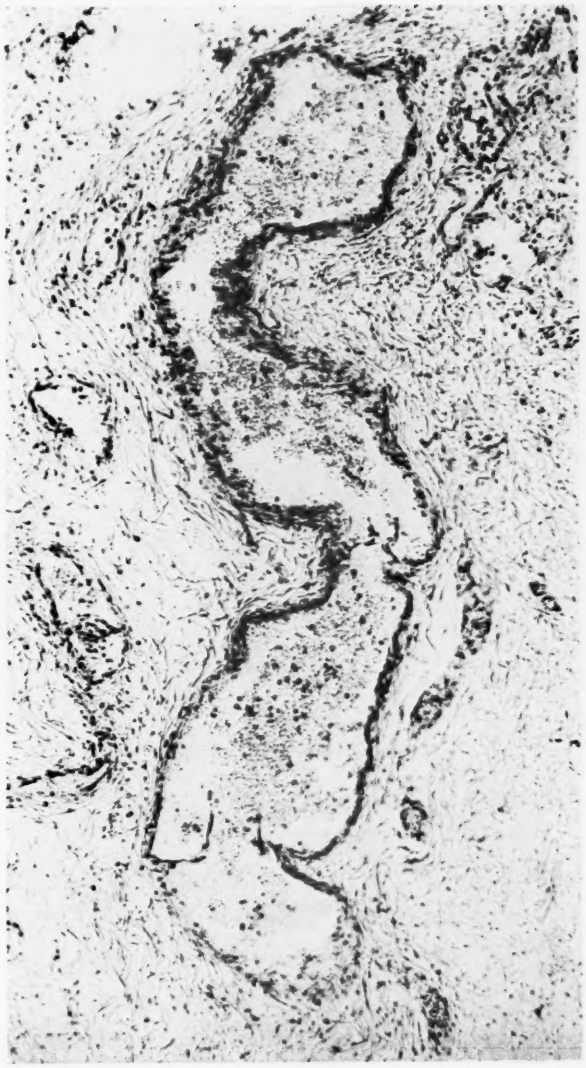

FIG. 10. Section of the efferent lymphatic after leaving the pulmonary side of the lymph node. It shows the position of two valves which open toward the hilum and, grossly, the character of the contents of the vessel. From the extreme left of the vessel as seen in figure 12. ×100.

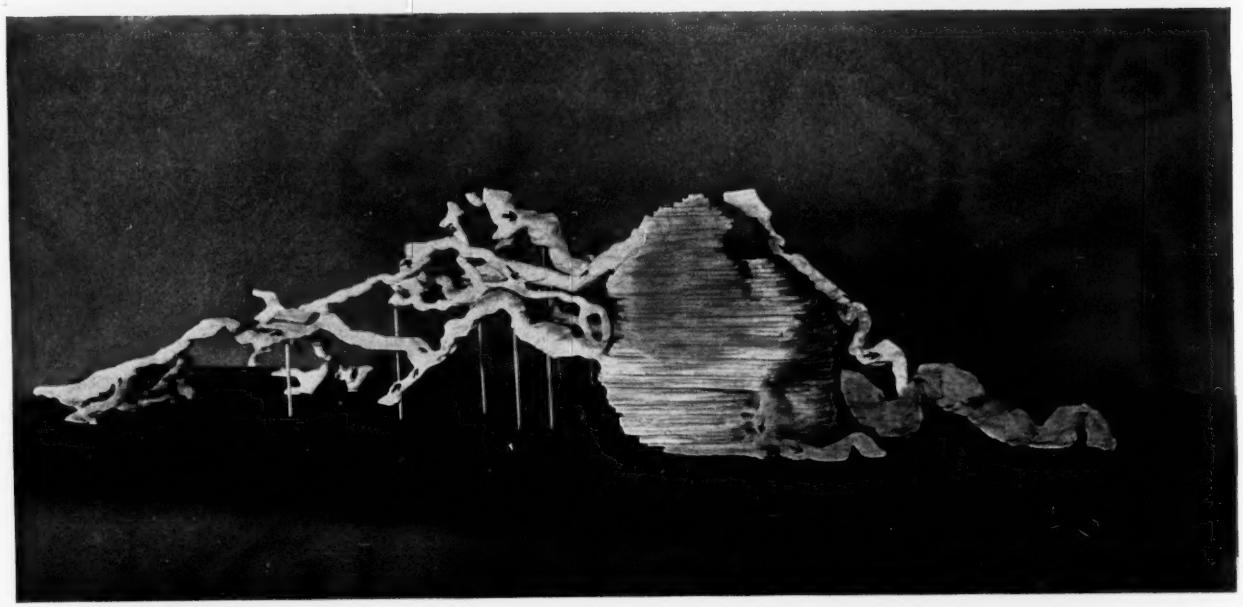

FIG. 11. The pleural side of the reconstruction. The lymphatics which carried the bacilli to the lymph node are *white*. The tubercle which was the source of the infection was situated in front of the angle formed by the two divergent arms of the white vessel. All the other afferent lymphatics are yellow. The tuberculous part of the node is *pink;* the nontuberculous part is *yellow*. The efferent lymphatics are *orange*. Note the lymphatic which emerges from the node near its centre and joins the efferent vessel leaving the node on its pleural side. The arrows indicate the direction of the lymph flow and, in general, the position of some of the valves. The lymphatic which joins the efferent lymphatic on its pulmonary side, and is colored yellow, is described in connection with figure 12. One-fourth the size of the reconstruction.

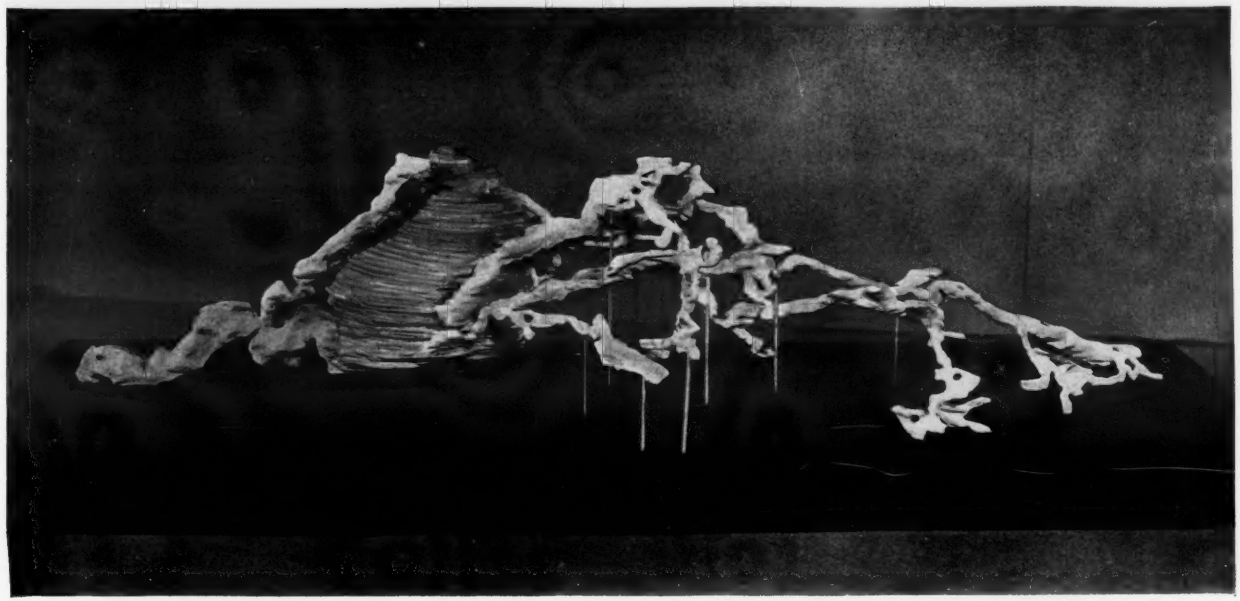

FIG. 12. The pulmonary side of the reconstruction. The color scheme is the same as in figure 11. The efferent lymphatic which leaves the pulmonary side of the node is *orange;* but the lymphatic which joins it is colored *yellow,* because it must have been connected with the pleural network of lymphatics at some point above the limit of the series of sections. One-fourth the size of the reconstruction.

on its pulmonary side, figures 11 and 12, was traced in the series of sections some distance above the level of the model; it did not pass out of the pleura, did not receive any branches, and was empty throughout its course (see figures 5 and 6). Although the connection could not be established, due to the fact that the lymphatics extended beyond the limit of the series, it apparently formed, with the afferent lymphatic nearest the node in figures 11 and 12, an arch over the pulmonary side of the node.

In tracing the focus from which the bacilli were conveyed to the lymph node, the position of the valves and the direction in which they opened, were of material assistance. None of the lymphatics which are colored yellow in figures 11 and 12 opened into that part of the node in which tubercles developed. Starting with the only lymphatic which was connected with the tuberculous portion of the node, it was traced through its course in the pleura until a lymphatic was found coming from the parenchyma of the lung, figure 3. The valve situated at this point immediately called attention to the lymphatic in the septum and it was then traced to the tubercle shown in figure 2.

Was this tubercle the only source of infection? To answer this question every lymphatic beyond the junction of the one coming from the tubercle in figure 2 with the pleural lymphatic was followed as far as the length of the series would permit. No other lymphatic than the one colored white in figures 11 and 12 could be traced to a tuberculous focus. It is possible that, had the series been more extensive (it consisted of 246 sections, 42 by 28 mm., and 40 micra thick), an additional focus might have been found. However, if an additional focus had been found, in order to gain access to the tuberculous portion of the node, the bacilli would have had to pass through the vessels already described.

There are three short lymphatics which form anastomoses between the white and yellow afferent lymphatics; however, the valves show that the lymph-flow was from the white to the yellow vessels.

As stated earlier in the paper, all the radicles of the two afferent systems colored yellow in figures 11 and 12 arise from or traverse active tubercles and also receive anastomosing lymphatics from the system colored white; yet, after entering the node, they do not give rise to tubercles though doubtless they contained bacilli. It is probable that the toxins contained in the sinuses derived from these lymphatics gave rise to the hyperplasia which makes up the lower portion of the node. Within the node the

tuberculous portion is separated from the nontuberculous (hyperplastic) portion by a well-defined trabecula, which apparently formed a barrier to the further extension of the tubercles.

SUMMARY

1. A small tuberculous lymph node situated in the pleura, forming part of the boundary of an *incisura interlobaris*, with its afferent and efferent lymphatics, is described.

2. The focus from which tubercle bacilli were conveyed to the lymph node, and the course of the lymphatics through which they passed, were identified.

3. Only in that portion of the lymph node which the lymphatic conveying the bacilli supplied were tubercles developed. The other lymphatics which entered the node formed a wide-open bypath through the node.

4. The toxins contained in this bypath, and the associated sinuses, gave rise to an intense hyperplasia of the lymphoid tissue in the remainder of the node.

5. The lymph-flow, as shown by the presence of numerous valves, was toward the pleura. This showed that the direction of lymph-flow described for other portions of the lung holds true in this situation; namely, that from a narrow zone around the periphery of the lung the flow is toward the pleura, while in other portions of the lung it is toward the hilum.

6. Beyond the lymph node the flow was through the pleural network of lymphatics to a hilum node which showed active lesions.

7. Lymphatics from other parts of the lung were seen entering the hilum node, showing that those described were not the only source from which it was infected.

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TUBERCULOSIS OF THE COMMON CROW

A Preliminary Study

CHARLES A. MITCHELL AND R. C. DUTHIE[1]

A careful review of the literature reveals very few reports of tuberculosis of wild animals or birds in their natural environment, and then only when raised under more or less artificial conditions in close association with domesticated animals or birds. Calmette (1) states that "Nowhere in the world is the disease [tuberculosis] observed among wild species of birds." Fox (2) gives a very clear account of the incidence of tuberculosis in wild animals and birds in captivity. An analysis of his autopsy records shows 274 cases in 1860 mammals (14.7 per cent, in 6 of 12 orders, and 219 cases in 3505 birds (6.2 per cent) in 14 of 20 orders. This indicates that practically all wild animals and birds are relatively susceptible to tuberculosis when confined and exposed to infection. Reigler (3) observed 5 cases of tuberculosis among crows (*Corvus vorax*) in captivity.

In February, 1928, we received at our laboratory 36 common crows (*Corvus brachyrynchos*) shipped from Western Ontario, where these birds were reported to be dying in large numbers from a disease simulating "ocular roup" as encountered in domesticated birds. At autopsy five of the crows were found to have fairly extensive and well-defined lesions of tuberculosis. In four of the five infected birds the lesions were confined mainly to the liver, with a very moderate invasion of the spleen; acid-fast bacilli were relatively few, and were short and comparatively plump. This type of microörganism is hereinafter referred to as *strain 1*. The remaining bird had extensive nodular tuberculosis of the spleen, three large nodular tubercles on the serous surface of the gizzard around its greater curvature, and numerous pin-point miliary tubercles in the liver. Acid-fast microörganisms were numerous, long, slender, and beaded. This microörganism is shown in the tables as *strain 2*.

During the present summer we have examined 4 crows (2 adults and 2 fledglings) captured locally. One adult male revealed a few small tu-

[1] Pathological Division, Health of Animals Branch, Department of Agriculture, Ottawa, Canada.

berculous lesions of the liver containing acid-fast microörganisms similar to those described as strain 1.

We have examined in all 40 crows, 6, or 15 per cent, of which have shown well-defined tuberculous lesions in which acid-fast microörganisms could be demonstrated.

Experimental Inoculations: Lesion inoculations were made from each of the two strains (or types) from the crows and then transferred from animal to animal. Results of cultural inoculation are not yet available. The data so far obtained are given in tables 1 and 2, which reveal points of special interest in regard to the pathogenicity of these strains.

STRAIN 1

Strain 1 is evidently an intermediary strain and is clearly pathogenic for chickens, guinea pigs and rabbits. After two passages through chickens it remains virulent for guinea pigs; for example, crow 1 to cock 1, to hen 4, to guinea pig O14, and after passage through the guinea pig it retains its pathogenicity for chickens,—guinea pig O14 to cockerel 770. It also appears less virulent for rabbits than for guinea pigs or chickens.

Tuberculin Reactions: Chickens and guinea pigs inoculated with strain 1, and tested with avian and bovine tuberculins, gave a well-defined reaction to avian tuberculin but were also sensitive in some degree to tuberculin prepared from bovine strains.

Isolation of Microörganism: Plants were made from the lung of cock 1, strain 1_1 on serum-agar and Dorset's egg. In about three weeks there developed on serum-agar a moderate growth having the moist slimy appearance of avian tubercle bacilli. This strain has been subcultured without difficulty on serum-agar and potato, but scarcely any growth has as yet been obtained on egg media. Stained smears on microscopic examination revealed minute, relatively short, acid-fast bacilli.

STRAIN 2

This strain inoculated into a chicken, a rabbit and a guinea pig, proved virulent for the guinea pig but practically avirulent for the chicken and rabbit. This chicken and guinea pig gave strong positive reactions to

TABLE 1

Tubercle-bacillus strain 1 of crow

ANIMAL NUMBER	SPECIES	DATE INOCULATED	INOCULUM	ROUTE	TUBERCULIN REACTIONS			DIED	DEATH	AUTOPSY FINDINGS
					Date	Bovine tuberculin	Avian tuberculin			
		1928			*1928*			*1928*	*days*	
1	Aged cock	February 27	Spleen of crow 1	Intraperitoneal	March 27	−	++	May 15	78	Right lung solid mass of small tubercles. Few miliary tubercles in wall of air-sac. Acid-fast microörganisms, numerous, short and plump
856	Guinea pig	February 27	Spleen of crow 1	Intraperitoneal	March 27	−	++	April 1	34	One small lesion in spleen. Short acid-fast bacilli.
857	Rabbit	February 27	Spleen of crow 1	Intraperitoneal	March 27	−	−	May 11	74	Coccidiosis. No evidence of tuberculosis
882	Guinea pig	April 1	Spleen of guinea pig 856	Intraperitoneal				April 14	13	Pneumonia
O1	Rabbit	May 15	Lungs of cock 1	Intraperitoneal				Killed August 14	91	Local lesion in floor of abdomen. Single tubercle in kidney. Scattered lesions in liver. Numerous small tubercles in lung. Acid-fast microörganisms, long and beaded
O2	Rabbit	May 15	Lungs of cock 1	Intraperitoneal				July 18	78	Lung and spleen moderately affected; pancreas extensively. Local lesion; short, plump acid-fast microörganisms

O3	Guinea pig	May 15	Lungs of cock 1	Intraperitoneal	July 31	+	+			Still living
O5	Guinea pig	May 15	Lungs of cock 1	Intraperitoneal	July 31	−	?	Killed August 11	88	Local lesion in abdomen. Few moderately large tubercles in spleen, liver, diaphragm and intestines
H3	Hen	May 16	Lung of cock 1	Intraperitoneal	July 13 July 31	++ +	++++ ++++	Killed August 10	85	Extensive miliary tuberculosis of spleen, liver, mesentery and wall of intestine. Short acid-fast bacilli numerous
H4	Hen	May 16	Lung of cock 1	Intraperitoneal				June 24	39	Left lung and greater part of right lung tuberculous. Spleen and mesentery extensive; liver slight. Short acid-fast microörganisms
O14	Guinea pig	June 25	Lung of H4	Intraperitoneal				July 10	15	Spleen very much enlarged. Pancreas shows extensive infection; liver moderate. Short, acid-fast microörganisms present
O30	Rabbit	July 10	Pancreas of guinea pig O14	Intraperitoneal						Still living
O31	Guinea pig	July 10	Pancreas of guinea pig O14	Subcutaneous	August 14	++	++++			Still living
O32	Guinea pig	July 10	Pancreas of guinea pig O14	Intraperitoneal				Killed August 14	35	Emaciated; liver shows numerous large discrete tubercles. Spleen enlarged and grayish
770	Cockerel	July 10	Pancreas of guinea pig O14	Intraperitoneal	July 31	++	++++	Killed August 14	35	Liver shows many small tubercles; spleen moderately affected

TABLE 2

Tubercle-bacillus strain 2 of crow

ANIMAL NUMBER	SPECIES	DATE INOCULATED	INOCULUM	ROUTE	TUBERCULIN REACTIONS			DIED	DEATH	AUTOPSY FINDINGS
					Date	Bovine tuberculin	Avian tuberculin			
		1928			*1928*				*days*	
2	Cock	February 27	Spleen of crow 2	Intraperitoneal	March 27 May 22	+++ +	− −	Killed June 25	122	2 small pin-point tubercles in liver
860	Guinea pig	February 27	Spleen of crow 2	Intraperitoneal	March 27	++	−	April 27	60	Miliary tubercles in spleen; mesenteric lymph nodes caseous; short acid-fast micro-organisms
892	Guinea pig	April 27	Spleen of guinea pig 860	Intraperitoneal				May 5	8	Pneumonia
893	Guinea pig	April 27	Spleen of guinea pig 860	Intraperitoneal				May 10	13	Pneumonia
894	Rabbit	April 27	Spleen of guinea pig 860	Intravenous and intraperitoneal				Killed July 13	77	No evidence of tuberculosis

Explanation of signs used: In chickens: Swelling of the injected wattle to 1½ times its normal thickness is indicated by one plus, (+); twice normal thickness by two plus (++), etc. *In guinea pigs:* A maximum or four plus (++++) reaction is one in which we find redness, oedema, infiltration and central necrosis, each of which is indicated by a plus sign.

bovine tuberculins but a negative response to avian tuberculin. In the case of chicken 2, the reaction tapered off and was negative at the time this bird was killed.

We were unfortunate in losing this strain in our guinea pigs through deaths from an intercurrent cage pneumonia. It is, however, significant that animals inoculated with this strain reacted to mammalian tuberculin only.

DISCUSSION

The incidence of tuberculosis in wild animals and birds in their natural state is largely a matter of conjecture and is governed in all probability by their relative chances of exposure rather than any marked lack of susceptibility.

In the case of the *Corvidae* and birds of similar habits contact with man and domesticated animals of course cannot be excluded. It is therefore conceivable that these birds might become infected in a number of ways through contact with tuberculous poultry, domesticated animals and their dejecta, infected waste-products from garbage dumps and country slaughter-houses, and the unburied carcasses of diseased animals. The susceptibility of the *Corvidae* to mammalian tuberculosis is at present unknown, but, granting that the susceptibility exists, it will readily be seen that opportunities for infection are by no means wanting.

The ability of the crow to transmit infection to other birds or animals remains to be shown.

Further work is being done along this line.

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PREGNANCY AND PULMONARY TUBERCULOSIS[1]

ARTHUR H. MORSE[2]

A review of the recent literature touching the question of the influence of the reproductive process upon pulmonary tuberculosis yields no satisfactory answer. Indeed, except for eclampsia, I am unaware of any clinical problem in obstetrics concerning which there is a more widespread diversity of opinion. It is impossible at present to state definitely the cause of this lack of unanimity, but its existence challenges us to further carefully controlled investigations.

In this paper I propose first to mention the most common theories which have been advanced to support the contention that the reproductive process as a whole deleteriously influences a coexistent pulmonary tuberculosis. Second, at the risk of repetition, I shall state briefly the outstanding clinical observations as set down during the past decade in the literature of France, Germany, and the United States, and shall outline the position of the Yale Woman's Clinic in this matter. I shall then consider certain factors which may explain the reason for the conflicting conclusions, and, finally, shall offer for your consideration certain suggestions which seem of importance as bearing upon future studies of this problem.

The first of the theories offered depends upon the upward displacement of the diaphragm associated with the enlargement of the uterus. The muscle in its higher position is said to diminish the capacity of the pleural cavities and to limit the expansion of the lungs, thus causing a slowing and decrease of the pulmonary circulation. While it would appear that the capacity of the lungs would be decreased under these circumstances, Dohrn has shown that this is not the case, since the diminished height of the pleural cavities is compensated by an increase in width. Moreover, Zuntz and Williams, in investigations upon the respiratory exchange during pregnancy, found that while there is no great increase in the

[1] Presented at a meeting of the Eastern Section of the American Sanatorium Association, Norwich, Connecticut, October, 1928.

[2] Division of Obstetrics and Gynaecology, Yale School of Medicine, New Haven, Connecticut.

consumption of oxygen, or decrease in the output of carbon dioxide, there is a great increase in the amount of air inspired.

From a clinical standpoint Gross also points out that this theory is open to error, since on the one hand an increase in the tuberculous process may occur in the first few months of pregnancy, when the diaphragm still occupies its original position, and, on the other, an improvement in the pulmonary lesion may occur in the second half of pregnancy in spite of the heightened position of this muscle. Moreover, as the result of an artificial pneumothorax the pulmonary circulation is disturbed, and in spite of these facts the patient is usually benefited. From the evidence, therefore, it appears that the theory is not generally applicable.

Significance is attached by some to changes in certain constituents of the blood. For example, a decrease in the lipolytic ferment is said to occur in pregnancy, the decreased lipolytic power leading to a lessened resistance as a result of the inability of the serum to dissolve the fatty or waxy substances of the capsule of the bacillus. This conclusion is open to question in the light of the findings of Slemons and Stander that the lipoid content of the blood is greatly increased during pregnancy. Furthermore, even though the lipolytic content were unchanged, there is no satisfactory evidence, from a bacteriological point of view, that these ferments act in any direct way upon the microörganism. Others are impressed by the striking increase in the cholesterin content of the blood during pregnancy, and suggest that the extension of the pulmonary infection depends upon the fact that the tubercle bacillus thrives more favorably upon a nutriment rich in cholesterin. This view is based upon experiments *in vitro*, but there is no evidence that a similar activity occurs in the body. Still others believe that the need for calcium by the developing foetus in the later months of pregnancy calls upon the calcified pulmonary nodules, thus leading to a dissolution of these structures and a dissemination of tubercle bacilli. Contrary opinions hold that, as a result of improved absorption and decreased excretion, a sufficient increase of calcium occurs fully to care for the foetal needs. In support of the latter view is cited the frequently observed presence of puerperal osteophytes on the inner surface of the skull and the new formations at the cartilaginous borders, particularly at the symphysis, of calcium-containing bony tissue.

The untoward influences of the puerperium are believed to depend in the first place upon the increased respiratory efforts associated with the second stage of labor, or to the sudden descent of the diaphragm

following delivery. These physiological changes, it is said, bring about a dissemination of bacilli from the upper to the lower portions of the lungs. In the second place, bacilli are thought to be transferred into the blood-stream of the uterus as a result, during the placental stage, of the tearing through of tuberculous foci situated in the *decidua basalis*.

All these theories have their proponents and opponents, but it appears that none of them satisfactorily explains why the process of gestation should influence a pulmonary lesion unfavorably.

Turning now from a consideration of these theoretical points to the results of clinical observation, we find in general that authorities fall into three groups:

1: Those who hold that in most cases of pulmonary tuberculosis pregnancy has an unfavorable influence, that in most instances of latent tuberculosis there is a flaring up and extension of the lesion, and that the puerperium is particularly to be dreaded. Such opinions are frequently expressed in statistical studies and in many recent obstetrical texts by the foremost German gynaecologists.

2: Those who believe that usually in pregnancy there is no progress of the pulmonary lesion but that, on the contrary, the latter remains stationary or even retrogresses during this period, that pregnancy fails to inaugurate a lighting up of the infection and that it has no unfavorable influence upon a lesion already stationary. Some in this group even go so far as to report the healing of cavernous processes during pregnancy.

3: Between these two extreme groups are those who in general regard the effect of pregnancy as unfavorable but who at the same time recognize the fact that in certain cases the lesion remains stationary or improves during gestation.

Of French observers, Bar, the eminent obstetrician, believes that pregnancy has an unfavorable effect upon pulmonary tuberculosis. In determining the method of treatment to be followed, he attaches great value to the character of the tuberculin reaction. For example, when in a woman with pulmonary tuberculosis in early pregnancy the tuberculin reaction is strong, he tends, always considering the findings in the lungs, to refrain from the induction of abortion and to depend upon medical treatment. On the other hand, if in a patient at a similar stage in pregnancy the reaction is negative, or of a feeble intensity disproportionate to the extent of the lesion present, he inclines to the termination of pregnancy, particularly if the pulmonary lesions have appeared synchronously with the onset of pregnancy.

In young women he prefers to empty the uterus by a therapeutic abortion, and believes that the optimal time for interference is realized when the patient is only slightly affected and when, if proper care is assured following the termination of pregnancy, the lesion will probably heal. In older women, in whom the lesion is more advanced, who have already had children, and in whom the risks associated with a subsequent pregnancy are great, he thinks hysterectomy advisable.

Rist believes that pregnancy in a tuberculous woman leads to an aggravation of symptoms, to the extension of existing lesions, to the production of fresh ones, and to the flaring up of those which are quiescent. Of 117 cases in which tuberculosis began either during pregnancy or shortly afterward, 60 died after two years, while 43 were still alive but in a serious condition, leaving little hope for recovery. In the 14 temporarily arrested cases, pregnancy was regarded as the determining cause of the onset of tuberculosis. The efficiency of therapeutic abortion as a means of arresting the course of pulmonary tuberculosis he thinks not sufficiently proved. He emphasizes the value of artificial pneumothorax, and advises its application in pregnant tuberculous women when the lesions are unilateral and when no extensive pleural adhesions are present. Of 40 patients in whom artificial pneumothorax was established during pregnancy or shortly after confinement, 14 were clinically well and 4 died. Rist takes an optimistic view regarding the woman who is clinically well following the performance of this operation, and believes that if bacilli are absent from the sputum over a period of two years, and if the temperature curve remains permanently normal, she may be permitted to become pregnant. In his opinion, however, the collapse of the lung should be maintained for at least six months after confinement.

Bernard, from a study of 327 female patients, found pulmonary tuberculosis more commonly in primiparae than in multiparae, and is convinced that the disease frequently either has its origin or becomes aggravated during pregnancy or after confinement. He regards therapeutic abortion as rarely indicated, provided the patient receives appropriate medical treatment. In fibrous phthisis the patient usually can be carried through pregnancy without great risk if she is properly cared for. Even in caseating tuberculosis he has seen favorable results by the institution of appropriate therapeutic measures, including pneumothorax.

Dumarest and Brette have seen patients in whom pulmonary tuberculosis was aggravated by pregnancy and by the puerperium, but, they have, on the other hand, been deeply impressed in several instances by

the apparently beneficial effect of pregnancy upon the tuberculous process. The induction of abortion is strongly condemned except in very rare cases in which the condition is extremely grave and the child is viable.

Couvelaire, of the *Baudelocque Maternité*, is unable to define his impression regarding the effect of pregnancy, labor and the puerperium upon the evolution of pulmonary tuberculosis. He is of the opinion that in the greatest number of cases of fibrous phthisis the influence of gestation is nil. On the contrary, in the progressive forms he sometimes observed during gestation, but more often during the puerperium, a more or less rapid exacerbation of the pulmonary lesion, which terminated fatally within one year in nearly half the cases observed. However, he feels unable to compare the evolution of the tuberculous process as he has observed it with such an evolution in nonpregnant women with the same forms of tuberculosis. In the treatment of these cases a conservative procedure was followed, since Couvelaire is not convinced of the therapeutic value of an induced abortion or of hysterectomy.

Finally, Pinard takes a conservative position. He is wholly opposed to the artificial termination of pregnancy and directs his attention to the supervision of the pulmonary lesion and the pregnancy.

A similar divergence of opinion obtains in Germany. Winter observed 138 tuberculous women, 93, or 67 per cent, of whom showed unmistakable aggravation of the lesion. In patients with latent or healed tuberculosis an activation of the pulmonary process occurred in only one-fifth of the cases, while in patients with an active lesion the process was uninfluenced by pregnancy in only 14 per cent. This authority holds that in latent or healed tuberculosis therapeutic abortion, except in unusual cases, is contraindicated. In active tuberculosis it is recommended at any stage of pregnancy up to the seventh month. In women still young, and in whom one may hope for a permanent cure, temporary sterilization may be the method of choice. In other instances Winter combines a vaginal hysterectomy with the interruption of pregnancy, thus not only sterilizing the woman but saving her a future periodical loss of blood during menstruation.

Pankow believes that therapeutic abortion offers the most hope when carried out early in pregnancy and at an early stage of the disease. Siegert takes a most radical position, and in 26 women in whom pulmonary tuberculosis was associated with gestation he has performed a supravaginal hysterectomy and a bilateral oöphorectomy.

Gross, while regarding the influence of gestation upon pulmonary tuberculosis as unfavorable, stresses the importance of sanatorium treatment. Therapeutic abortion, in his opinion, is justified only upon medical indications, as, for example, when in the first trimester of pregnancy sanatorium treatment has proved unsuccessful.

On the other hand, Schultze-Rhonhof, from a study of the statistical returns from Baden, Prussia, Bavaria and Hesse, was unable to draw any definite conclusion regarding either the influence of pregnancy upon pulmonary tuberculosis or the best method of treatment. Finally, Menge is of the opinion that either the reputed unfavorable influence of pregnancy upon pulmonary tuberculosis does not exist or is overestimated.

Of American obstetricians, Norris, because of his long and intimate association with the Henry Phipps Institute in Philadelphia, has had an extended experience with tuberculous women in whom the pulmonary lesion was complicated by pregnancy. Over a period of nine years this observer examined all patients of this group who applied to the institution for treatment. The physical and bacteriological examinations were performed by skilled internists and careful records were taken of the pulmonary condition, the weight and the general health. An endeavor was also made to follow the patient after the puerperium. As a result of this study, Norris believes that no observer can fail to be impressed with the unfavorable influence often exerted by pregnancy on the course of pulmonary tuberculosis. He points out, however, that each patient must be studied individually. Thus, occasionally women with advanced tuberculosis first seen in the middle or later months of pregnancy withstood well the test of the later months of pregnancy, labor and the puerperium, and at six or nine months after delivery they were at least as well as they were at the 6th or 7th month of pregnancy.

Norris is of the opinion that tuberculous women should not become pregnant unless the pulmonary lesion is in the first stage and has been quiescent for a minimum period of two years. He believes it as yet impossible to determine with certainty which patients will bear the added strain of pregnancy well and which badly. Moderately extensive lesions, recent activity, the development of secondary lesions, especially laryngeal involvement, loss of weight, fever, haemorrhage, sweats, lack of vigor, and inability to obtain proper medical treatment, are ill omens, whereas the reverse is more favorable.

Norris advises that prior to the fifth month the uterus should be emptied if the disease manifests evidence of becoming active, or if the

lesions are extensive, or if laryngeal involvement occurs. Curettage during the first six or eight weeks, and in the later cases vaginal hysterotomy, are as a rule the preferable methods. Interruption of pregnancy does not ensure an amelioration of the pulmonary condition but does definitely improve the prognosis. In this observer's experience about 65 to 70 per cent of patients in the first five months of pregnancy will be definitely improved by the emptying of the uterus as soon as acute symptoms arise, provided the proper after-treatment is carried out. Sterilization is rarely justifiable.

After the fifth month of pregnancy it is generally advisable to treat these patients expectantly. Labor should be made as easy as possible. To ensure this induction of premature labor two weeks before term is often advisable; rarely, if ever, should they be allowed to go beyond term. During labor forceps or version is usually indicated.

Bridgman and Norwood, on the other hand, take a conservative position. From an analysis of 14,000 histories from the indoor obstetrical department of the Johns Hopkins Hospital, they found 134 women who were grouped as having pulmonary tuberculosis in one or more of its various forms. This number roughly corresponds to the morbidity percentage of Baltimore City as obtained from the Health Department. In other words, the physical examinations by the obstetrical staff of the Johns Hopkins Hospital, according to these figures, suggest an incidence-rate of tuberculosis closely approximating that reported by the physicians of the city, which it is believed is definitely below the actual figures. The authors feel justified in drawing from such small numbers only suggestive conclusions as to the effect of pregnancy on the morbidity percentage, but point out that this population of 14,000, equally divided between white and colored women, and including a large number of multiparae, shows no increase over the expected incidence of pulmonary tuberculosis during gestation. Although they believe that gestation and the puerperium may serve as a final factor to break down patients who have tuberculosis, they can find no evidence that pregnancy in any way promotes the incidence-rate. They point out, also, that when it is remembered that the child-bearing age of women corresponds to that age-period in which pulmonary tuberculosis ordinarily appears, even without pregnancy, and that the incidence-rate at this age is definitely below the male incidence-rate, except between the ages of 20 and 30, the question is raised whether the association of tuberculosis and pregnancy has not been exaggerated and whether it is not in great part

coincidental. If it be conceded that tuberculosis in adults is the development of a disease contracted in childhood, then it would appear that, though gestation may precipitate activity of tuberculous lesions, the actual incidence-rate of tuberculosis is not higher for women who have borne children than for those who have not. However, reliable statistics on the relation in incidence-rate of tuberculosis between pregnant and nonpregnant women are still lacking.

Bridgman and Norwood stress the need for protracted rest in bed in the case of women with pulmonary tuberculosis, but point out that, even if such treatment were possible in every case, there would always be a definite percentage of patients whose lesions are so overwhelming, or in whom the resistance is so low, that they would die. In their opinion, the risks of pregnancy are definitely increased by tuberculosis, depending to some degree on the type of lesion. However, they are of the opinion that, provided the household duties can be controlled, additional rest obtained, and the lesion is of the fibroid type and has been quiescent for at least three years, the risk of pregnancy may be assumed.

In the case of a pregnant woman in whom active tuberculosis is found, they stress the importance of intensively treating the tuberculosis, preferably in a sanatorium, and disregarding the pregnancy. Artificial termination of pregnancy is not indicated, since the excitement, the etherization, and the shock of the operation are additional factors which curtail the patient's strength at a most critical period. On the other hand, they regard as a wholly different matter an operation for sterilization carried out at a later period when the tuberculosis has become quiescent. To permit a tuberculous mother to be subjected to repeated pregnancies, with repeated recrudescences of an old lesion, is, in their opinion, unjustified.

Hill, from a comparison of the histories of 160 women whose pregnancies accompanied or immediately preceded their tuberculosis with those of their close controls at one year and at two years after diagnosis, and in the case of the pregnant women after conception or confinement, comes to the conclusion that pregnancy has no appreciable bearing upon the progress of the tuberculous disease.

Fishberg believes that in early cases of tuberculosis marriage should be postponed until information is available as to the course the disease tends to take. On the other hand, he regards the indiscriminate prohibition of marriage and maternity for tuberculosis patients as unjust. Women with chronic forms of tuberculosis may marry, for those with such forms

of the disease, as well as those in whom the disease is quiescent or has been arrested, bear maternity with impunity. As a result of statistical studies, he states that in about 20 per cent of cases an aggravation of the pulmonary lesion occurs soon after pregnancy, but about the same percentage of tuberculosis patients who do not become pregnant show exacerbations of the disease during the two-year period which pregnancy and lactation involve.

The position of the Yale Woman's Clinic is similar to that of Norris. While regarding the reproductive process as physiological, we realize that even in a nontuberculous woman a pregnancy which seems to be progressing normally may, as the result of metabolic disturbances or other complications, become abnormal. We believe it unjustifiable for a woman with an active pulmonary lesion to assume this additional risk. We have not hesitated, after consultation with a specialist in pulmonary disease, to terminate the pregnancy.

We prefer to empty the uterus not later than the fifth month of pregnancy. If artificial termination is carried out in the first weeks it can be completed at one sitting by a dilatation of the cervix, followed by curettage. If the pregnancy has advanced beyond this point, we regard a vaginal hysterotomy, particularly in primiparae, as the operation of choice. This is a relatively conservative procedure, since the pregnancy is terminated at one sitting and the uterus remains *in situ*. While packing of the cervix with gauze, in order to induce softening and dilatation, is applicable in certain cases of multiparae, the procedure predisposes to infection and generally necessitates the administration of a subsequent anaesthesia in order to empty the uterus completely.

We rarely employ ether as an anaesthetic. This long ago was replaced in our clinic by gas-oxygen and ethylene. If for any reason the administration of these gases is contraindicated, we may in suitable cases employ spinal anaesthesia. In our experiences no notable disturbances result either from the administration of the anaesthetic or because of the operative manipulations.

We do not interfere in the case of patients already in the second half of pregnancy, for we see no advantage to the patient from the induction of premature labor. On the other hand, we believe in shortening the second stage of labor by the application of forceps or by version and extraction, and in the third stage guarding carefully against excessive bleeding.

In the case of multiparous women upon whom we have performed

therapeutic abortion or who have been delivered spontaneously, we usually advise sterilization under gas-oxygen, ethylene, spinal or local anaesthesia at a later date, when the pulmonary lesion has become quiescent. In all patients we emphasize the necessity of sanatorium treatment subsequent to the obstetrical procedure.

On the other hand, we follow a conservative course in the case of pregnant women with a quiescent lesion, but we insist that such individuals be constantly under the supervision of a specialist in tuberculosis and a competent obstetrician.

As a result of this review, we cannot fail to be impressed by the international conflict of opinion in this matter. Various factors apparently contribute to the situation. Thus, Norris and Landis have pointed out that in most instances pregnant women with pulmonary tuberculosis are delivered either by midwives or by general practitioners, while only a relatively small proportion are seen by specialists. It follows naturally that the specialist is called in consultation in the worst cases and that the most desperately ill cases are likely to be sent to the obstetrical service of a hospital for delivery. Consequently, the obstetrician is most likely to see those patients who are doing badly, and this fact doubtless plays a rôle in the high mortality and morbidity as generally reported in this condition. Gross states that a similar factor plays a part in the discrepancies which appear in the German reports.

Gross, Schultze-Rhonhof, and Norris emphasize the danger of drawing conclusions from a small series of cases. Not only should a large series of patients be studied, but they should be carefully followed throughout pregnancy and for months following delivery. Statistics compiled from obstetrical services, from which patients are discharged in two or three weeks after delivery without subsequent careful supervision, are misleading because no history can be obtained of exacerbations which may occur during the puerperium and the period of lactation.

Bridgman and Norwood point out the significance of the difference in social and financial status of patients. Certain individuals are so situated that the burden of their household duties prevents them from taking sufficient rest. These patients, in whom the pulmonary lesion is just kept in check while they are doing their daily work, will be unable to prevent its advance if pregnancy is superadded. On the contrary, others are so constituted and financially situated that they are able to avail themselves of the best possible means of combating the associated lesion.

Another important factor in the minds of many observers is the medical

practitioner's unfamiliarity with obstetrics and the obstetrician's lack of training in the diagnosis of thoracic lesions.

In such a gathering as this, it would seem almost invidious to conclude by offering suggestions regarding future methods of investigation of the effect of the reproductive process upon pulmonary tuberculosis. However, if we are to make accurate observations and are to approach a uniform conclusion regarding this question, it will be necessary, in studying the problem, to reduce all variable factors to a minimum.

As has been emphasized above, the first requisite in this direction is to include a large number of cases which can be observed over an extended period, for the results obtained from the restricted observation of a small number of patients are misleading. It would seem necessary, also, to review these patients in groups, the division of the groups being based upon the character and extent of the pulmonary lesion and upon the duration and normal or abnormal character of the pregnancy.

In this connection, the condition of the individual patient should be emphasized. For example, given two women in the first trimester of pregnancy with a pulmonary lesion of equal activity and extent, the outcome would certainly be influenced unfavorably in her whose general resistance was lowered by continued nausea, vomiting, and inability to take food. Likewise, in the latter half of pregnancy, in one of a group of equally infected individuals, a similar untoward influence might depend upon a cardiac or renal complication necessitating the eventual termination of pregnancy by operative delivery.

The establishment in such a study of uniform conditions of nutrition and hygiene is important. The woman poorly nourished and obliged to work constantly to the end of pregnancy is less able to combat the pulmonary infection than the patient so situated that she can avail herself of every means in this direction. To compare results in such patients without taking these living conditions into account is faulty.

As a final requisite, the study should be undertaken as a coöperative effort on the part of trained specialists in pulmonary diseases and of competent obstetricians.

For several years a coöperative investigation along these lines has been in progress abroad. Since 1921 Couvelaire of the *Baudelocque Maternité*, which is in permanent connection with antituberculosis dispensaries in Paris, has employed a special ward and organization for the care of tuberculous women throughout pregnancy, labor, and the puerperium. Menge has undertaken a similar study in Germany. In connection with

his University Woman's Clinic is an isolation pavilion for the prolonged observation and treatment of pregnant tuberculous women. These patients are supervised by an internist, a specialist in tuberculosis, and an obstetrician, who are assisted by a roentgenologist.

As far as I am aware, there are few, if any, opportunities of a similar nature in this country, but I believe it would be worth while to inaugurate certain centres for a concentrated investigation of this problem. If, in our own State, all pregnant tuberculous women could be sent to a single sanatorium, admissions should be sufficiently large to offset any criticism regarding numbers. Having been hospitalized, these patients could then be carefully studied along the lines I have suggested by specialists in tuberculosis and by competent obstetricians, sent to a designated hospital for obstetrical care, and then returned to the sanatorium for further observation.

I recognize that such a plan involves expense and certain other difficulties, but without question the results from a carefully controlled coöperative investigation of this kind would, in a few years, yield reliable information of great value to the immediate patient and to the pregnant tuberculous woman of the future.

SUMMARY

1. Attention has been called to the most common theories advanced to support the contention that the reproductive process as a whole deleteriously influences a coexistent pulmonary tuberculosis.

2. The relevant outstanding clinical observations which have appeared in the literature of France, Germany, and the United States during the past decade have been reviewed.

3. Certain factors are considered which may explain the reason for the conflicting conclusions regarding the influence of pregnancy upon pulmonary tuberculosis.

4. Certain suggestions are offered which seem of importance as bearing upon future studies of the problem.

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ACUTE SUBAPICAL VERSUS INSIDIOUS APICAL TUBERCULOSIS

A Preliminary Report[1]

BRUCE H. DOUGLAS, MAX PINNER AND BEN WOLEPOR

For the last two or three years the European, and notably the German literature, has been replete with reports pronouncing the necessity of a change in some of the essential concepts in the pathogenesis of pulmonary tuberculosis. The time-honored teaching of its apical inception with insidious symptomatology, and of the slow and gradual apicocaudal progression, has been assailed from many angles. Under this concept, both diagnostic and therapeutic endeavors were concentrated upon apical lesions, allegedly the source of all evil, barring relatively few exceptional cases of acute and subapical onset, which were frequently the subject of special reports emphasizing their atypical nature. If the clinical study of pulmonary tuberculosis had become a specialty, apical diagnosis had become a special branch of it, with a refinement of diagnostic array and specific methods to the point where normality and pathological findings merged into a border-land in which subjective interpretation ruled supreme. Experienced clinicians, more so than the representatives of the special guild, had frequently warned of the superrefined apical diagnosis and accused the public sanatoria, in Germany in particular, of housing a large percentage of patients with imaginary or insignificant apical lesions.

The actual attack on the old doctrine occurred essentially from two distinct sides: (1) the clinical and prognostic significance of definitely demonstrable apical lesions was studied, and (2) the actual beginning of the clinical disease, "progressive destructive pulmonary tuberculosis," was investigated. As to the first point, Braeuning (10), in a study of patients with apical tuberculosis over a period of 7 years, found that only 7.8 per cent had developed progressive disease. This author emphasizes that progressive phthisis, as a rule, does not develop from

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

apical tuberculosis. If all phthisis would develop from apical lesions, the latter would have to be 50 times more frequent than the former, while the dispensary service showed nearly equal numbers for both types of disease. Only 2.6 per cent of apical lesions showed tubercle bacilli in the sputum during an observation of 3 years, while in 81 per cent of open cases the disease was of 3 years' duration or less. Of 125 patients with productive tuberculosis, Turban I and II, 118 were able to work after 3 years.

Lydtin (28), on a similar material of 450 patients, arrived at an almost indentical figure, and quite recently Kayser-Petersen (23) reported that, out of 120 sanatorium patients in the first stage of the disease, only 7.6 per cent had developed progressive tuberculosis or died of the disease after a period of 15 years. Haudek (17), on the basis of an unusually extensive roentgenological experience, claimed that apical tuberculosis is "overdiagnosed," both in regard to its frequency and its significance. Long-extended observation, according to the same author, shows that apical lesions usually do not progress, that strictly apical cavities are rare, and that the few apical cavities usually originate below the apex. He has never seen the roentgenological picture of a fibrocaseous, bronchogenic phthisis develop from an apical focus; truly incipient phthisis always shows uninvolved apices. Hochstetter (18) observed no progressive disease in 23 apical foci during an observation period of 10 to 14 years; Redeker (32) states that he does not know of any serial X-ray observations to demonstrate the development of apical foci into progressive apicocaudal phthisis.

More or less identical points of view are represented by many prominent observers whose names will be mentioned presently in another connection. Careful clinical observation had led the French School of Bard and Pièry and its followers, notably Rist and Bernard, to differentiate clearly the benign apical tuberculosis. Based on a similar foundation W. Neumann emphasizes the same distinction. Neisser (29) has coined the term *tuberculosoid*, and Hollo (19) the term, *juvenile phthisis*, for types of disease which, in their opinion, practically never progress to destructive disease.

If the evidence against apical lesions as the incipient stage of phthisis is strong, how does phthisis begin? This question is answered by the recent work in which the names of Assmann (1), Redeker (31), Romberg (35), Ulrici (39), and many others are prominent. Assmann (1) described, first in 1922, infiltrative processes in the infraclavicular region

in young adults. He interpreted these lesions as a truly incipient stage of pulmonary tuberculosis. Without discussing in detail the chronological development, the present-day status may be briefly summarized: A probably bronchogenic reinfection in allergic individuals causes a usually small infiltrative (presumably bronchopneumonic) focus. This lesion, known in the German literature as *Assmann focus*, *infraclavicular infiltration*, or *early infiltration* (*Frühinfiltrat*), is an acute and truly incipient lesion. Its most frequent localization is the infraclavicular region, but any other part of the pulmonic fields may be affected, apical localization being extremely rare. Clinically its appearance is accompanied by a sudden onset of mostly very slight catarrhal, grippe-like symptoms. In a number of cases no symptoms are noted. The temperature may or may not be elevated; the pulse-rate is usually increased. The important point is that its symptomatology bears no resemblance whatsoever with the textbook symptoms of "incipient tuberculosis." Cough is frequently absent in the beginning; the symptoms, slight as they may be, do not begin insidiously; lassitude, fatigue, backache, night-sweats, loss in weight, all these, are symptoms of a later stage. The physical signs are so uncharacteristic,—frequently absent according to competent observers,—that a correct diagnosis cannot, in some instances, be made without X-ray studies. This lesion contains all the potential sequellae of pulmonary tuberculosis. It may resorb so completely as to leave no roentgenological mark; it may caseate and excavate, giving rise to a usually spherical, isolated cavity (the *Frühkaverne* of the German authors); it may give rise to bronchogenic metastases (*Ausstreuungstuberkulose*); it may, by way of the two last-mentioned possibilities, develop into a progressive and destructive fibrocaseous tuberculosis, which then, in its turn, usually progresses downward. At this point it is important to mention, that according to many observers the apices become involved frequently as soon as actual progression and destruction ensue. The chain of developments, as outlined here, may be interrupted at any phase: the infiltrated area may fibrose before excavation sets in, the *Frühkaverne* may heal by fibrosis, cirrhotic processes may halt further progression at any stage. The early lesion is characterized,—and herein lies its enormous practical significance,—by its instability. Whatever development occurs, it occurs rapidly; significant and detectable changes are noted within a few weeks' time.

These developments have been described by many authors: Assmann

(1), Redeker (31), Unverricht (40), Ickert (21), Bacmeister (7), Baer (8), Brauening (10), Brecker (12), Gassul (15), Haudek (17), Hollo (19), Lydtin (29), Pischinger (30), Dorendorf (13), Rehberg and Zürcher (34), Warnecke (41), Romberg (35), Kausch and Klingenstein (22), (24), Ulrici (39), and others. The only author, who, to our knowledge, has written on this subject in English, so far, is Fishberg (14). Wessler (42), as Fishberg pointed out, described infraclavicular infiltrations. The possible merit of having recognized these lesions as the most important incipient manifestation of pulmonary tuberculosis belongs to Assmann (1) and Redeker (31).

The authors mentioned above are far from agreeing on some essential points. Some, most emphatically represented by Redeker (33), claim that every true phthisis (that is, progressive, destructive pulmonary tuberculosis) begins with an acute subapical infiltration, that isolated apical foci practically never progress, that no causative relation exists between the two types of lesions. Apical tuberculosis, when it gives rise to symptoms, must be treated as a clinical entity *per se;* but it is irrelevant in phthisiogenesis.

Another group of workers, led by Assmann (6), warns not to overrate the significance of these newer findings. They doubt the exclusive rôle that the early infiltration is supposed to play in phthisiogenesis; they emphasize, notably Simon (38), the significance of apical lesions in this regard.

A third group of authors, Schroeder (37), fully supported by most pathologists, such as Graeff (16), Huebschmann (20), Loeschke (25), Schmincke (36), Beitzke (9), profess adherence to the old teaching of the apical beginning.

The occurrence of the "early infiltration" cannot be doubted. Several points of controversy, however, remain to be settled: (1) In what percentage of phthisis is an "early infiltration" the actual beginning? (2) What, if any, is the relation of isolated apical foci to the "early infiltration?" The pathologist claims that in practically all cases of phthisis old apical foci are present, that almost invariably the most destructive, and presumably oldest lesions are found in the apices. But the final result of a destructive process is hardly amenable to an analysis of its incipient phase. A patient whose autopsy was performed in this institution recently proved this point clearly. The first available X-ray film shows uninvolved apices, and only a small, isolated round infraclavicular

cavity on the right side. At autopsy, a little more than two years later, the apparently oldest and most destructive lesion was a large cavity in the left apex. For obvious reasons pathologicoanatomical studies on the early phase are lacking. Assmann (5) described only one autopsy finding of an infraclavicular infiltration. It was an exudative pneumonic focus of the size of a cherry, centrally caseated and surrounded by productive nodules. The description is incomplete, no mention being made of the apices.

Most of the reports on this subject are based on clinical observations, following the development of definite cases. The truly incipient infiltration is relatively seldom observed since it is so fleeting in character. In the far-advanced cases of pulmonary tuberculosis a retrospective analysis of the development is extremely difficult or impossible. An apical involvement, occurring shortly after the excavation of the original infiltration, can probably not be distinguished from an apical focus preceding the acute subapical lesion, neither on the X-ray film nor on the postmortem table. It must be considered, too, that an acute infiltration may be superimposed, casually unconnected, upon an apical focus. It will be of particular importance to determine whether this combination is more frequent than the occurrence of the "early infiltration" in persons without demonstrable apical foci. The available evidence shows that even in the presence of old apical foci, the appearance of an "early infiltration" marks an essentially new turn in the disease. In other words, and regardless of possible connections, the "early infiltration" is a distinct clinical entity. From the epidemiological and preventive point of view, this questionable causal relation is of paramount importance. If further studies confirm the relative clinical insignificance of apical foci, they still may play an important epidemiological rôle.

It is obvious that clinical observation alone can hardly elucidate the problem of phthisiogenesis, and in particular determine the relative frequency of one or the other type of incipiency. It is hopeless,—and with these newer claims more hopeless than ever,—to recognize a considerable percentage of truly incipient lesions. The bulk of patients still come for diagnosis with a disease well past the stage of incipiency.

Confronted with these difficulties and with a problem which appears of an unusually acute importance for all practical tuberculosis work, we decided to attempt an analysis of our sanatorium patients in regard to the points mentioned. Our idea was to correlate the history of each patient with the findings on his first available X-ray film.

PERSONAL STUDIES

The data collected for this study were as follows:

I. History
  1. Date of onset
  2. Duration from onset to first X-ray picture
  3. Type of onset
  4. Course since onset

II. X-ray interpretation
  1. Extent of involvement
  2. Presence and localization of cavities
  3. Apical involvement

The date of onset can be easily determined in a considerable percentage of patients in whom symptoms were unequivocal; in others very careful questioning and sound judgment are required to determine with any degree of certainty the probable date of onset, particularly so in patients with neurasthenic symptoms, low intelligence and with a multiplicity of diseases. The duration of the disease from the onset to the date of the first available X-ray film is an arbitrary period because it may represent any fraction of the duration of the whole disease. The only significant period would be from onset until death, but this would leave out all non-fatal cases. By correlating the duration of symptoms up to the time of entrance to the sanatorium (which is the time at which the X-ray films were taken) with the extent of the lesion, significant data were obtained. Under the heading, "Type of Onset," several subheadings were used. In the following tabulation only three groups, in combination with "the Course since Onset" are used. For this investigation the salient point was to determine any symptomatology which may be referred to the "early infiltration." We classified the patients accordingly in three groups: (1) those having a sudden onset, (2) those having not a sudden onset and no acute symptomatology at any time since the onset, and (3) those having not a sudden onset but acute exacerbations some time following the onset.

In the X-ray interpretation the extent of the lesions was classified according to "Diagnostic Standards," with the exception that cavities were not considered. In other words, the mere extent, regardless of the presence of cavities, was the determining factor for classification. The presence or absence of cavities was noted, regardless of size, number or character; in regard to localization only two classes were made, namely,

"cavity in apex" and "cavity below apex." In cases in which both localizations occurred, the case was counted under the first heading. In regard to "apical involvement" it was necessary to make three classes: (1) apices free; in this group are included cases which showed slight pleural shadows over the apical fields, but none that had any demonstrable parenchymal involvement; (2) apices involved; this group contains all cases with definite parenchymal involvement in one or both

TABLE 1

Crude data

	NUMBER OF PATIENTS	PERCENTAGE OF TOTAL
I. Onset and course:		
1. Sudden onset	105	52.5
2. Insidious course	48	24.0
3. Insidious onset; later acute exacerbations	47	23.5
Total	200	100.0
II. Extent of involvement:		
1. Minimal	21	10.5
2. Moderately advanced	54	27.0
3. Far advanced	125	62 5
Total	200	100.0
III. Apical involvement:		
1. Apices free	45	22.5
2. Apices involved	119	59.5
3. Apices relatively free	36	18 0
Total	200	100.0
IV. Cavities:		
Present	142	71.0
In apex	24	16.9 (of all cavity-bearers)

apical fields; (3) apices relatively free; this group comprises two essentially different types of cases, namely, those in which a subapical lesion extends only slightly into the lower part of the apical field, in which, however, the centre of involvement is definitely subapical; and those cases in which one or both apices show an involvement which is very slight in comparison with more extensive and more destructive processes in subapical regions.

The present report is based on 200 patients.

Results

In table 1 are shown the crude data: the large number of patients with sudden onset should be noted, and the relatively few patients who had an insidious course throughout.

In the following tables, the attempt is made to correlate particularly two characteristics, namely, apical involvement, and the presence or absence of acute symptoms with the other data collected.

TABLE 2

Relation between apical involvement and course of disease

	APICES INVOLVED (119 PATIENTS)		APICES FREE (45 PATIENTS)		APICES RELATIVELY FREE (36 PATIENTS)	
		per cent		*per cent*		*per cent*
Sudden onset	36	30.3	43	*95.6*	26	72.2
Insidious course	44	36.9	0	*0.0*	4	11.1
Insidious onset; later, acute exacerbations	39	32.8	2	4.4	6	16.7

TABLE 3

Relation between apical involvement, duration of symptoms, and course of disease

DURATION OF SYMPTOMS	ALL PATIENTS			PATIENTS WITH SUDDEN ONSET			PATIENTS WITH INSIDIOUS COURSE		
	Number of patients	Apices involved		Number of patients	Apices involved		Number of patients	Apices involved	
			per cent			*per cent*			*per cent*
6 months and less	33	8	24.2	27	4	14.1	4	3	75.0
More than 6 months to 2 years	86	43	50.0	49	16	32.7	20	17	85.0
More than 2 to 5 years	48	37	77.1	17	6	35.3	14	14	100.0
More than 5 years	33	31	93.9	12	10	83.3	10	10	100.0
Total	200	119	59.5	105	36	34.3	48	44	91.7

In table 2, to mention only the obviously significant figures, it is shown that free apices occur practically only in patients with sudden onset, whereas apical involvement occurs with almost equal frequency in the three groups.

In the first column of table 3 it is shown that the frequency of apical involvement increases with the duration of the disease; this increase is particularly marked in patients with sudden onset (column 2), while patients with insidious course (column 3) have a high frequency of apical involvement throughout the course of the disease. Roentgenologically

demonstrable apical lesions in patients with sudden onset are a late development.

Table 4 presents an affirmation of the conclusion reached from the preceding table: uninvolved apices in patients with sudden onset occur with decreasing frequency with increasing duration of disease.

In table 5 the same general relation is expressed in the average duration of symptoms. It is undoubtedly significant that 44 patients with apical involvement and with an insidious course have had symptoms for nearly

TABLE 4

Relation of duration to the frequency of uninvolved apices in patients with sudden onset

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	APICES FREE	
			per cent
6 months and less	27	18	66.7
More than 6 months to 2 years	49	18	36.7
More than 2 to 5 years	17	5	29.4
More than 5 years	12	2	16.7
Total	105	43	41.0

TABLE 5

Relation of apical involvement to average duration of symptoms and to course of disease

	APICES FREE		APICES INVOLVED	
	Number of patients	Average duration of symptoms	Number of patients	Average duration of symptoms
		years		*years*
Sudden onset	43	*1.51*	36	3.49
Insidious course	0		44	*4.35*

three times as long a period before entering the sanatorium as patients with uninvolved apices and sudden onset.

Table 6 demonstrates the fact that a patient with sudden onset is much more likely to develop cavitation early in the disease than a patient with an insidious course. In the former group of patients the incidence of cavities is high, and at approximately the same level of frequency throughout the disease; in the latter group there is a definite increase of cavitation with increase of duration. The greater likelihood of cavitation in the former group is emphasized by the fact that after an average duration of 2.22 years 68.6 per cent of patients have cavities, while in

the insidious group the incidence is 58.3 per cent after nearly double the duration, 4.08 years.

The participation of each of the three clinical types in the production of cavities is shown in table 7. Of all cavity-bearers, more than one-half belong to the group with sudden onset, although this group, as shown in the preceding table, represents a much shorter average duration of dis-

TABLE 6

Relation of course of disease to presence of cavities and duration of symptoms

DURATION OF SYMPTOMS	SUDDEN ONSET			INSIDIOUS COURSE		
	Number of patients	Cavities present		Number of patients	Cavities present	
			per cent			*per cent*
6 months and less	27	22	81.5	4	1	25.0
More than 6 months to 2 years	49	29	59.2	20	14	70.0
More than 2 to 5 years	17	12	70.6	14	7	50.0
More than 5 years	12	9	75.0	10	6	60.0
Total	105	72	68.6	48	28	58.3
Average duration of symptoms	2.22 years			4.08 years		

TABLE 7

The distribution of 142 cavity-bearers according to clinical course of disease

DURATION OF SYMPTOMS	TOTAL NUMBER OF PATIENTS	SUDDEN ONSET		INSIDIOUS COURSE		INSIDIOUS ONSET WITH ACUTE EXACERBATIONS	
		Number	Percentage of total	Number	Percentage of total	Number	Percentage of total
6 months and less	27	23	85.2	2	7.4	2	7.4
More than 6 months to 2 years	62	38	61.3	14	22.6	10	16.1
More than 2 to 5 years	33	12	36.4	7	21.2	14	42.4
More than 5 years	20	9	45.0	6	30.0	5	25.0
Total	142	82	57.8	29	20.4	31	21.8

ease. The prevalence of this group over the combined other two groups is particularly striking in patients during the first half-year of their disease. The close dependence of the development of cavities on acute clinical symptoms is shown by the fact that only 20 per cent of cavities are found in patients with an insidious course throughout. The percentage of cavity-bearers increases in the third group with the duration of the disease, indicating that most of the cavities developed after acute

manifestations. The percentage of cavity-bearers in the first group decreases with the duration, indicating a high mortality of cavity-bearers within the first two years.

Table 8 demonstrates again the relation between the course of disease and the presence of cavities, but divided into the patients with and without apical involvement. The difference in the percentage-incidence of cavities in the various groups becomes significant if compared with the average duration of the disease. The last four tables emphasize the

TABLE 8

Relation of course of disease to presence of cavities and apical involvement

	SUDDEN ONSET			INSIDIOUS COURSE			ALL PATIENTS			AVERAGE DURATION OF SYMPTOMS
	Number of patients	Cavities present		Number of patients	Cavities present		Number of patients	Cavities present		
			per cent			*per cent*			*per cent*	
Apices involved	36	28	77.8	46	25	54.3	119	78	65.5	4.43
Apices free	43	33	76.8	0			45	34	75.6	1.51
Average duration of symptoms	2.22 years			4.08 years						

TABLE 9

Relation of duration of symptoms to extent of lesion

DURATION OF SYMPTOMS	NUMBER OF PATIENTS	FAR ADVANCED	
			per cent
6 months and less	33	20	60.6
More than 6 months to 2 years	86	60	69.8
More than 2 to 5 years	48	32	66.7
More than 5 years	33	13	39.4
Total	200	125	62.5

fact that cavitation should not be considered a late occurrence in patients with sudden onset.

Table 9 demonstrates the fact that the extent of lesions is by no means a function of the duration of the disease. The percentage-incidence of far-advanced processes is approximately the same at any chronological stage of the disease. It is undoubtedly true that in the individual patient the extent of the lesion increases in time, but the far-advanced stage is very frequently reached rapidly, that is, within six months. Only a small percentage of patients with sudden onset remain minimal or

moderately advanced for any length of time and reach the third stage at a later time. In the meantime a certain number of patients have died one or two years following the onset; this explains the percentage-decrease of far-advanced patients after more than two years' duration.

In table 10 the same data are analyzed separately for patients with sudden onset and with insidious course. There is a high percentage of far-advanced lesions in the former group throughout the disease, and a

TABLE 10*

Relation of duration of symptoms to extent of lesion and course of disease

DURATION OF SYMPTOMS	SUDDEN ONSET			INSIDIOUS COURSE		
	Number of patients	Far advanced		Number of patients	Far advanced	
			per cent			*per cent*
6 months and less	27	23	85.2	4	2	50.0
More than 6 months to 2 years	49	43	87.7	20	16	80.0
More than 2 to 5 years	17	15	88.2	14	8	57.1
More than 5 years	12	10	83.3	10	5	50.0
Total	105	91	86.5	48	31	64.5
Average duration of symptoms	2.22 years			4.08 years		

*In this table all patients having cavities, regardless of the extent of the lesion, are added to the group of far advanced lesions by extent only.

TABLE 11

Relation between course of disease and apical involvement

	SUDDEN ONSET (105 PATIENTS)		INSIDIOUS COURSE (48 PATIENTS)		INSIDIOUS ONSET; LATER, ACUTE EXACERBATIONS (47 PATIENTS)	
		per cent		*per cent*		*per cent*
Apices involved	36	34.3	44	*91.7*	39	82.8
Apices free	43	40.9	0	0.0	2	4.4
Apices relatively free	26	24.8	4	8.3	6	12.8

lower level in the latter with a very suggestive drop after more than two years' duration. The total percentage of far-advanced cases, compared with the respective duration in each group, shows a striking difference in favor of the sudden group.

In table 11 is shown the fact that practically all patients with insidious onset have apical involvement, and none have entirely uninvolved apices. This table should be compared with table 2; then it becomes

evident that free apices occur almost exclusively in patients with sudden onset, and that an insidious course leads almost invariably to apical involvement. This double set of relations deserves particular attention.

Table 12 represents the distribution of far-advanced lesions according to the three types of clinical course. It should be noted that more than one-half of far-advanced cases belong to the group with sudden onset and that a very high percentage of cases with sudden onset is found in

TABLE 12

The distribution of 125 far-advanced lesions, according to clinical course of disease

DURATIONS OF SYMPTOMS	NUMBER OF PATIENTS	SUDDEN ONSET		INSIDIOUS COURSE		INSIDIOUS ONSET, LATER ACUTE EXACERBATIONS	
			per cent		*per cent*		*per cent*
6 months and less	20	16	80.0	2	10.0	2	10.0
More than 6 months to 2 years	60	36	60.0	13	21.7	11	18.3
More than 2 to 5 years	32	12	37.5	8	25.0	12	37.5
More than 5 years	13	9	69.3	3	23.1	1	7.6
Total	125	73	58.4	26	20.8	26	20.8

TABLE 13

Some significant data for cases of acute subapical and of insidious apical tuberculosis

	TOTAL NUMBER	SUDDEN ONSET AND APICES FREE		INSIDIOUS COURSE AND APICES INVOLVED	
		Number	Percentage of total	Number	Percentage of total
Far advanced within 6 months' duration	13	12	92.3	1	7.7
Far advanced within 1 year's duration	18	15	83.3	3	16.7
Far advanced regardless of duration	49	25	51.0	24	49.0
Cavities present within 1 year's duration	25	20	80.0	5	20.0
Cavities present regardless of duration	58	33	56.7	25	43.3
Average duration of symptoms		1.51		4.35	
Number of patients		43		44	

the early course of disease. In a similar way as in table 7 the third group gains numerical significance in the later stage of the disease. The assumption seems justified that processes leading to far-advanced involvement (and cavitation, as shown in table 7) produce acute symptoms in the vast majority of patients.

Since it was shown before that a close relation exists between "uninvolved apices" and "sudden onset," and between "apices involved"

and "insidious course," the patients showing both characteristics in each group, are represented in table 13. The significance of these data is obvious.

Table 13 shows that the characteristics "apices free" and "sudden onset" have a definite predilection for adolescents and young adults.

COMMENT

Before discussing the significance of the data presented, a few critical remarks in regard to the methods used in this study must be mentioned. A great deal of reliance had to be based upon anamnesic data. We are aware of their inherent uncertainty. Since all the emphasis rests upon the question of whether acute manifestations were present at some time

TABLE 14

Age-distribution of the different types of clinical course and of apical involvement

AGE OF PATIENTS	SUDDEN ONSET		APICES FREE		INSIDIOUS ONSET		APICES INVOLVED	
	Number	Percentage of total	Number	Percentage of total	Number	Percentage of total	Number	Percentage of total
19 years or less	28	26.6	11	24.4	9	18.8	24	20.2
19.1–25 years	52	49.5	25	55.6	11	22.9	48	40.4
25.1–31 years	17	16.2	7	15.6	12	25.0	22	18.4
31.1–37 years	3	2.9	1	2.2	7	14.6	15	12.6
37.1–43 years	3	2.9	1	2.2	4	8.3	5	4.2
More than 43 years	2	1.9	0	0.0	5	10.4	5	4.2
Total	105	100.0	45	100.0	48	100.0	119	100.0

during the disease or not, the probability of errors is not very great. It is more likely for a patient in retrospect to create in his memory a period of insidious symptoms leading up to the dramatic start of his disease than to forget it, if it was present. Such mistakes would have minimized the difference shown throughout this study between the two main groups of patients.

Another objection may be raised, namely, against the fact that the clinical status of each patient was interpreted on roentgenological evidence alone. Such a procedure would, of course, be totally unjustified in judging the condition of a given patient, but for this study only extent and localization of lesions, and absence or presence of cavities, were to be determined. For this limited purpose, the interpretation of X-ray films assures probably the highest degree of uniformity.

The most serious point of criticism is the relatively small number of patients who were investigated. For this reason, this communication is called a preliminary report; the same type of study is being continued on a larger group of patients. On the other hand we feel that some of the results are of definite practical significance and that they should be reported in order to draw wider attention to the problems involved.

In most of the tables the two intermediary groups of patients, namely, those with "apices relatively free" and those with "insidious onset and later acute manifestations" have been omitted, because of the smallness of the groups and because the apparently significant data are evident in the other groups. Patients with "apices relatively free" represent in no way a homogeneous group; here we have essentially those cases in which small apical foci have been followed by advanced lesions in other parts of the lung, and those cases in which subapical lesions have begun to involve parts of the apical fields.

In regard to the type of onset, clinical observation teaches that the majority of all "early infiltrations" start suddenly, though frequently with slight symptomatology; a small number of patients with early infiltrations have no symptoms whatever for insidious general symptoms. This puts some cases with "early infiltrations" in the group with insidious onset, where, theoretically, they do not belong. On the other hand, some acute symptoms may be referred to tuberculosis which are caused by intercurrent diseases; this would put patients with a truly insidious course in a group in which they do not belong. For all these reasons the actual figures are probably less clear cut than they would be if all possible errors could be eliminated.

What are, then, the actual conclusions which can be drawn from this study?

1: Sudden onset is not less frequent in pulmonary tuberculosis than is insidious onset. (Table 1.)

2: Apical involvement is not a characteristic of incipiency, but it occurs in the majority of cases after the incipient stage has passed. (Tables 3 and 4.)

3: The extent of the lesion does not bear a direct relation to the duration of the disease. Of all patients reaching the far-advanced stage, the majority do so within the first half-year. (Tables 9, 10 and 12.)

4: Cavitation is not a late occurrence; its frequency is nearly the same at any stage of the disease. (Tables 6 and 7.)

5: Apical involvement bears a close relation to the type of the clinical course. (Tables 2 and 11.)

6: An analysis of patients with pulmonary tuberculosis as to the two characteristics "apices involved" and "type of onset" leads to the differentiation of two different clinical types of disease. (Table 13.)

Their *extreme* representatives can be briefly characterized as follows:

		Type 1	*Type 2*
Onset:			
	1. Clinically	Sudden	Insidious
	2. Anatomically	Acute, bronchopneumonic infiltration	Discrete, productive tubercles
	3. Localization	Subapical	Apical
Course:			
	1. Clinically	In acute exacerbations	Slow progression or long periods of standstill
	2. Anatomically	Rapidly progressive or retrogressive changes interrupting chronic course	Very slow changes
	3. Direction of progression	Toward apices and apicocaudal	Apicocaudal
	4. Extent of lesion	Large extent already in "incipient stage"	Incipient stage identical with minimal stage
	5. Cavitation	Very early occurrence	Late occurrence if ever
	6. Duration	Relatively short	Very long

Our second type is more or less in conformity with the usual textbook description of pulmonary tuberculosis; the second type, heretofore frequently described as an "atypical" form, shows significant deviations. The two types cannot be clearly differentiated solely by the characteristics "apical involvement" and "type of onset," because apical involvement occurs in the majority of patients with early infiltrations in the later stages of the disease and because some of these patients have no suddenly beginning symptomatology. In our series all patients with "apices free" belong probably to type 1; the same thing is probably true of all patients with sudden onset, and of those patients who have reached the far-advanced stage within one year after the onset of symptoms; this would make about 135 patients as contrasted with 48 patients whose symptomatology is strongly suggestive as belonging to type 2.

The numerical preponderance of the acute type of tuberculosis warrants much more attention than it has usually received. To recognize it early is therapeutically most important. To do so it is necessary to acquire an orientation which is greatly at variance with the usual teachings given to students, to practitioners, and particularly to the public. The entire set of so called typical symptoms of tuberculosis are charac-

teristic only of the apical type; in the sudden type they occur only after the stage of incipiency is well passed. During the incipient stage there is no (or very slight) cough, no lassitude, no loss of weight, no fatigability; the symptoms do not unnoticeably creep upon the patient. They appear suddenly and simulate a "touch of grippe," an "acute cold," or a bronchopneumonia. The apices, being usually uninvolved at this stage, will not tell the story on percussion and auscultation; without X-ray examination a number of diagnoses will fail. Whether a patient with apical tuberculosis comes to treatment a few months or a year after the inception of his disease, is probably of little import in most cases, while the patient with an early infiltration usually has lost his best chances during the same length of time.

This then, is the first conclusion of this study: early infiltrations must be detected in the stage of true incipiency. The application of the usual diagnostic methods,—symptomatology and physical signs as taught for the diagnosis of apical tuberculosis,—fails in this regard.

A second conclusion refers to the development of pulmonary tuberculosis. The type with sudden onset is likely to reach the stage of "far advanced" within a few weeks. It cannot be emphasized too much that for this type "incipient" and "minimal" are not interchangeable terms. Wide extension and extensive cavitation develop within periods of time to be counted by weeks. After the first acute phase there begins frequently a period of relative quiescence, during which resorption and fibrosis usually occur. It is during this second act of the disease that the "typical symptoms of incipient tuberculosis" are noticed. But now the lesion has well passed the minimal stage. This fact explains in part the failure to find at any time a sufficient number of "minimal" cases to account for the number of "far advanced" ones. This type of patient is in the minimal class only during an exceedingly small part of his disease; for the largest part of the duration of his disease he is far advanced. The concept of a slow apicocaudal progression cannot explain this course. Our figures seem to indicate that the fate of a patient belonging to type 1 is decided within the first six months after the onset of the disease. Marked progression, such as infiltration of new territory, caseation, and excavation, is at any stage of the disease an acute phenomenon, both clinically and morphologically. All destructive changes in tuberculosis are acute processes; the apparent chronicity of the disease is due to the continuous attempts of the body to adapt itself to the established damage. This viewpoint is borne out by the observation that

only 20 per cent of all cavity-bearers, and only 20 per cent of far-advanced patients, have never noticed any acute symptoms.

There remains the question of the relation between apical involvement and early infiltration. Whatever the frequency may be with which patients with apical tuberculosis develop an early infiltration, the latter must be considered as a clinical entity *per se*, as the beginning of a new chapter in the history of the disease. Regardless of an apical involvement preceding an acute infiltration, the latter alone determines all further development. It is difficult to determine from our data how frequently apical involvement preceded an infiltrative process.

Of 119 patients with apical involvement, 36 had sudden onset; it is highly probable that they developed apical involvement after the incipient stage. Of the remaining 83 patients, forty-four had an insidious course throughout, indicating that no "early infiltration" intervened. This leaves 39 patients in which the symptomatological development would indicate the sequence of apical involvement—acute infiltration; of these 39 patients, 19 are far advanced. Of these, some may have started with an early infiltration without noticeable symptoms. In summary: Out of 200 patients, probably less than 19 have developed far-advanced lesions, starting probably with apical involvement and developing later an acute infiltrative process.

How frequently do apical lesions, without the intervention of acute infiltrations, develop into far-advanced lesions? According to orthodox teaching, this mechanism is the usual development of far-advanced phthisis; according to Redeker (32), it never occurs. We have in our series 44 patients with apical involvement and insidious course; only 30 per cent of them having one year's duration are far advanced; after an average duration of 4.35 years slightly more than one-half are far advanced. In other words, out of 125 far-advanced cases, only 24, that is, less than 20 per cent, are at all likely to belong to the slowly progressing, apicocaudal type of pulmonary tuberculosis. The fact that the frequency of far-advanced lesions is greater during the earlier part of the disease than later, makes it probable that processes with sudden onset and with insidious symptomatology have been included in this group. This would reduce the number of progressive apical lesions still further; their relative insignificance is clearly expressed in tables 7, 12 and 13.

After all is said, about 40 apical lesions *may* have developed into far-advanced processes, less than 19 with, and less than 24 without the inter-

vention of acute infiltration. This occurred among a total of 125 far-advanced lesions. These figures are much higher than analogous reports in the literature. The discrepancy is undoubtedly due in large part to the fact that our studies are based entirely on sanatorium material. This institution has permanently a long waiting-list. It is reasonable to assume that, of all patients with apical tuberculosis, we see particularly those whose disease has taken a turn toward the worse. But the fact that such developments do occur should be a warning against the tendency of many modern writers to assign to apical lesions practically no significance in phthisiogenesis.

The conclusions of this statistical presentation would be open to justified doubt, if they could not be supported by clinical observation. The literature, quoted in the beginning of this report, contains an abundance of such proof. Among our own patients we have observed all the processes which we must assume to occur on the basis of this statistical survey. A detailed discussion of these developments does not belong in this paper. We wish to mention, however, that our X-ray files and clinical records contain plentiful material to show all those developments whose occurrence must be concluded from our tables. The most important ones, some of which run counter to the traditional teaching, are:

1: The development of far-advanced lesions with cavitation within a period of six months.
2: The presence of acute infiltrative lesions in the infraclavicular region with perfectly clear apices.
3: Apical involvement occurring some time after the appearance of subapical processes.
4: A history of insidious symptoms, with physical and roentgenological findings of small, productive, apical tuberculosis, suddenly followed by acute symptomatology and the appearance of exudative subapical foci.
5: Apical tuberculosis, at times with marked but never suddenly beginning symptoms, existing during a number of years without evidence of progression.

We do not have any serial X-ray records to show the slow and gradual development of an extensive and destructive tuberculosis from strictly apical lesions. Whenever apical lesions were followed by progressive disease, the inception of the latter was marked by acute symptoms, and the rapid development of exudative foci. It must remain for further studies to determine the nature and the relative frequency of apical lesions developing into progressive tuberculosis.

SUMMARY

1. Progressive and destructive pulmonary tuberculosis usually begins *suddenly*, with *exudative subapical* lesions.

2. Strictly apical productive tuberculosis is not, as a rule, the incipient stage of progressive and destructive pulmonary tuberculosis; it may precede the latter; but even in such cases the latter starts usually as stated under *1*. The rôle which apical tuberculosis plays in phthisiogenesis is rather insignificant as compared to that of acute subapical infiltrations.

3. Lesions far advanced as to extent, and excavations, frequently develop within less than six months.

4. Processes leading to active progression and to excavation are most frequently associated with acute symptoms.

5. Apical involvement is, in the majority of patients, not an occurrence of incipiency but a late development.

6. Diagnostic and therapeutic endeavors must be directed primarily toward the acute, subapical processes, and not toward the insidious apical disease.

7. Physical signs and symptomatology, traditionally described as characteristic for "incipient pulmonary tuberculosis," are misleading for the detection of truly incipient subapical acute processes.

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RECURRING NONTUBERCULOUS PNEUMONIA RESULTING FROM CYSTIC OVERFLOW[1,2]

EVERETT MORRIS AND CHARLES P. HARROD[3]

A primary tumor-growth in a bronchus, or in the mediastinum or pleura gives rise to few or no symptoms in its early stages. Its accidental discovery is often the result of search made for another disease, usually tuberculosis. In the case to be presented the problem has been to disprove the presence of tuberculosis from which the patient presumably had been suffering since her marine service, February, 1919, and to determine, if possible, the cause for an unusual series of respiratory symptoms and pathological changes. Unusual interest in this case grows out of the long-drawn-out period of intermittent disability covering a period of nine years, the regularity of attacks and the uniformity of symptoms, the marked displacement of the mediastinum, the absence of typical râles during the attacks of pneumonia, and finally the comparative freedom from this disabling condition over long intermittent periods.

CASE HISTORY

D. L., yoemanette, second class, U. S. Navy; age 38; enlisted September, 1918; prewar occupation, milliner. *Family and Personal History*: Good; no history of aspiration of foreign body. Influenza in October, 1918, and pneumonia in February, 1919; treated in a United States Naval Hospital and discharged from service March, 1919, with a respiratory disability. During 21 months in four government hospitals was treated three times for haemoptysis. From January, 1922, to May, 1923, patient was not hospitalized, during which time she suffered from four severe pulmonary haemorrhages. Entered training to study stenography May, 1925.

The first emergency admission, November 14, 1925, was at Camp Kearney, California. The patient suffered from haemoptysis but no evidence of pulmonary tuberculosis was found. It is interesting to note that the red-cell

[1] Presented before the Clinical Section at the twenty-fourth annual meeting of the National Tuberculosis Association, Portland, Oregon, June 20, 1928.

[2] Published with the permission of the Medical Director of the U. S. Veterans' Bureau who assumes no responsibility for the opinions expressed or the conclusions drawn by the writers.

[3] United States Veterans Bureau Hospital, San Fernando, California.

sedimentation time was 240 minutes to 12 mm. Our laboratory considers 120 minutes as the minimal normal.

Radiological Examinations (C. P. H.)

Interpretation of Film 1: December 23, 1920 (figure 1). There is an abnormal area of increased density occupying approximately one-third of the lung-field zone between the 1st and 3rd costal cartilages, right side. The right diaphragm is slightly elevated, due to adhesions in the inner half. There are no findings suggesting tuberculosis.

Interpretation of Film 2 and Fluoroscopic Examination: November 18, 1925 (figure 2). The area above referred to is somewhat smaller, more circumscribed, lobulated, located anteriorly and appears to displace the trunks leading to the apex. The parenchyma of the lung appears clear. This mass moves synchronously with the respiratory movements.

Interpretation of Film 3: April 13, 1926 (figure 3). No change from the previous film aside from the mass appearing more opaque with the lobulations less prominent.

On June 15, 1926, at San Fernando, California, a diagnosis of a benign intrathoracic tumor on the right side was made. Patient was discharged on the same day and readmitted as an emergency December 30, 1926. Her temperature was 102°F., pulse 108, and respirations 30. She complained of pain in right side, harassing cough and fatigability. Said present illness began with severe chill 48 hours prior to admission. Also said that she had suffered from four similar attacks, varying in time from three to six months.

Physical Examination

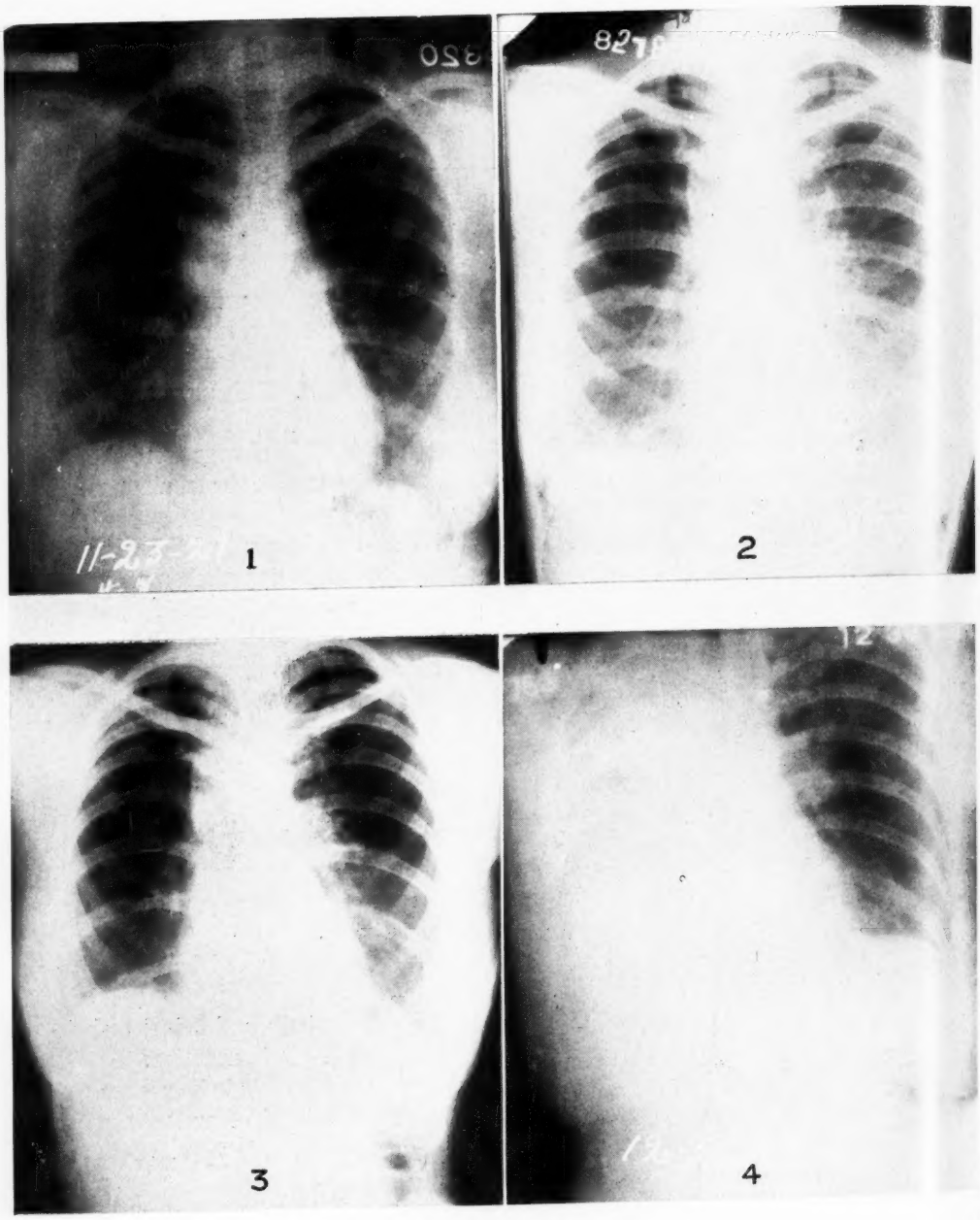
White; looked ill; face flushed; well developed and nourished. Chest long and fairly broad; right side practically immoble. Blood-pressure 105/70. Height 66 in.; best weight in past year 130 lbs.; present weight approximately 125 lbs. Abdomen, bones, joints and muscles negative.

Chest: *palpation:* fremitus, right, slightly increased over upper lobe. Left, slightly increased over upper lobe.

Percussion: Right, marked dulness from base to 2nd rib and 6th dorsal spine; less marked from 2nd rib and 6th dorsal spine up. Left, negative.

Auscultation: Right, whispered pectoriloquy over the 2nd interspace. Increased whispered voice, 3rd dorsal spine up. Diminished and absent breath-sounds from base to 4th rib and 6th dorsal spine. No râles. Left, exaggerated breathing throughout.

The oral cavity, throat and nose were normal.



FIGS. 1 TO 4

For description and interpretation see text

Repeated Radiological Examinations

Interpretation of Film 4: December 30, 1926 (figure 4). Fairly uniform density throughout the right side, obscuring the mass and the right diaphragm, and suggesting a pneumonia with questionable pleural effusion.

Interpretation of Film 5 (Bedside): September 8, 1927 (figure 5). Homogeneous density throughout the right chest, obscuring the mass and the diaphragm, and suggesting a pneumonia with a probable pleural effusion. Mediastinum not displaced.

Laboratory Findings

The urine and faeces were normal. Red blood cells 5,100,000; haemoglobin (Dare) 60 per cent; white blood cells 18,600; polymorphonuclears 78 per cent; lymphocytes 14 per cent; mononuclears 7 per cent; and transitionals 1 per cent. The blood Wassermann reaction was negative. Ten certified sputum examinations were made, all of which were negative for tubercle bacilli. Pneumococci, type IV, were reported. From March 12 to April 27, twelve guinea pigs were inoculated with antiforminized sputum, and a negative report for tuberculosis was made on all animals.

Diagnosis

Diagnosis was made of pneumonia, lobar, acute; also under observation for pulmonary tuberculosis. The acute pneumonic process terminated by crisis on the seventh day. From March 30 to April 7th the patient suffered from a series of small pulmonary haemorrhages, the total amount of which was 700 cc. The patient left the hospital May 4, 1927, against medical advice.

Readmission to Hospital

During the interval of four months between this discharge and the next and last emergency admission, September 6, 1927, the patient had enjoyed fairly good health until seven days ago, when she became acutely ill from a chill, fever, pain in the chest, and an exasperating cough.

On this admission her clinical picture was more serious than the last. Her temperature was 103°F., pulse 110, and respiration 28. She showed evidence of more toxicity and less resistance.

Physical Examination

September 6, 1927. *Palpation*: Fremitus, right, slightly increased over upper lobe. Left, negative. *Percussion*: Right, dull from base to 4th rib and 6th dorsal spine; impaired resonance above this area. Left, negative. *Auscul-*

tation: Right, increased whispered voice from 4th rib and 6th dorsal spine up. Diminished and absent breath-sounds from base to 4th rib and 6th dorsal spine. No râles. Left, compensatory breathing throughout.

Laboratory Findings

Red cells 4,400,000; haemoglobin (Sahli) 75 per cent; white blood cells 23,600; polymorphonuclears 81 per cent; lymphocytes 14 per cent; and mononuclears 5 per cent. There were 8 certified negative sputum examinations for tubercle bacilli. Cultures showed the presence of pneumococci, streptococci, Friedländer bacilli and Micrococcus catarrhalis. The pneumococci were of type IV. A diagnosis was made of pneumonia, lobar, recurrent, type IV, and pleurisy, serofibrinous, acute. A crisis occurred on the eighth day.

Five additional guinea pigs were inoculated with certified antiforminized sputum with negative results. Cultures to grow blastomyces, aspergillus, oidium, monilia, and sporothrix were unsuccessful. The basal-metabolic rate was minus 14. The red-cell sedimentation time on date of last admission, September 7, 1927, was fifteen minutes, on November 7 sixty minutes, and on February 17, 1928, one hundred and twenty minutes. It dropped to eighty minutes on March 10, following a series of pulmonary haemorrhages.

Physical Examination

November 4, 1927. Patient complained of the following: Pain in the right chest, which was more or less continuous and was affected by weather conditions; fatigue syndrome; a nonproductive, "brassy" cough; and dyspnoea with occasional noisy respiration on exertion. Dyspnoea following slight exertion has been present since first illness. At times the cough was emetic. No changes in the pupils were noticed.

Percussion: Right: There was moderate dulness from the base to 3rd rib and 6th dorsal spine; less marked from 3rd rib and 5th dorsal spine up. Limited mobility of diaphragm. Left, slightly hyperresonant. *Auscultation*: Right: Increased whispered voice 3rd rib and 3rd dorsal spine up, with whispered pectoriloquy and bronchial breathing over the 1st and 2nd interspaces at the edge of the sternum and above the 3rd dorsal spine. Diminished breath-sounds from base to 3rd rib and 5th dorsal spine, and bronchovesicular breathing over same area. No râles or succussion sounds. Left: Exaggerated breathing throughout. Whispered pectoriloquy and bronchial breathing above the 3rd dorsal spine, probably transmitted. D'Espine's sign present. Heart-sounds normal. The circumscribed area of whispered pectoriloquy and bronchial breathing in the right upper lobe showed varying degrees of intensity at subsequent examinations. Absence of these signs have also been noted.

From March 8 to 12 of this year the patient again suffered from a series of pulmonary haemorrhages, the total amount being 1039 cc. of blood.

Radiological Examinations

Interpretation of Film 6: September 17, 1927 (figure 6). Trachea and mediastinal shadow displaced slightly to the right; right diaphragm obscured. There has been a marked clearing over the previous film; the mass is indistinct, due to the heavy density in that area, and the increased hilum shadow with an unresolved pneumonic exudate at right base. Mediastinum displaced slightly to the right.

Interpretation of Film 7: February 15, 1928 (figure 7). Trachea, heart and mediastinal contents markedly displaced to the right. The mass is more displaced laterally and higher in the chest, with a narrow area of increased density extending outward and upward from the hilum, forming the lower and outer limits of the lobulated mass. Displacement of mediastinum to right more marked, suggesting a massive collapse.

Interpretation of Film 8: June 7, 1928 (figure 8). This film shows a small puddle of lipiodol at or near the bifurcation. The remainder of the lipiodol entered the left lung and not the right lung, although this was the dependent side at the time of injection.

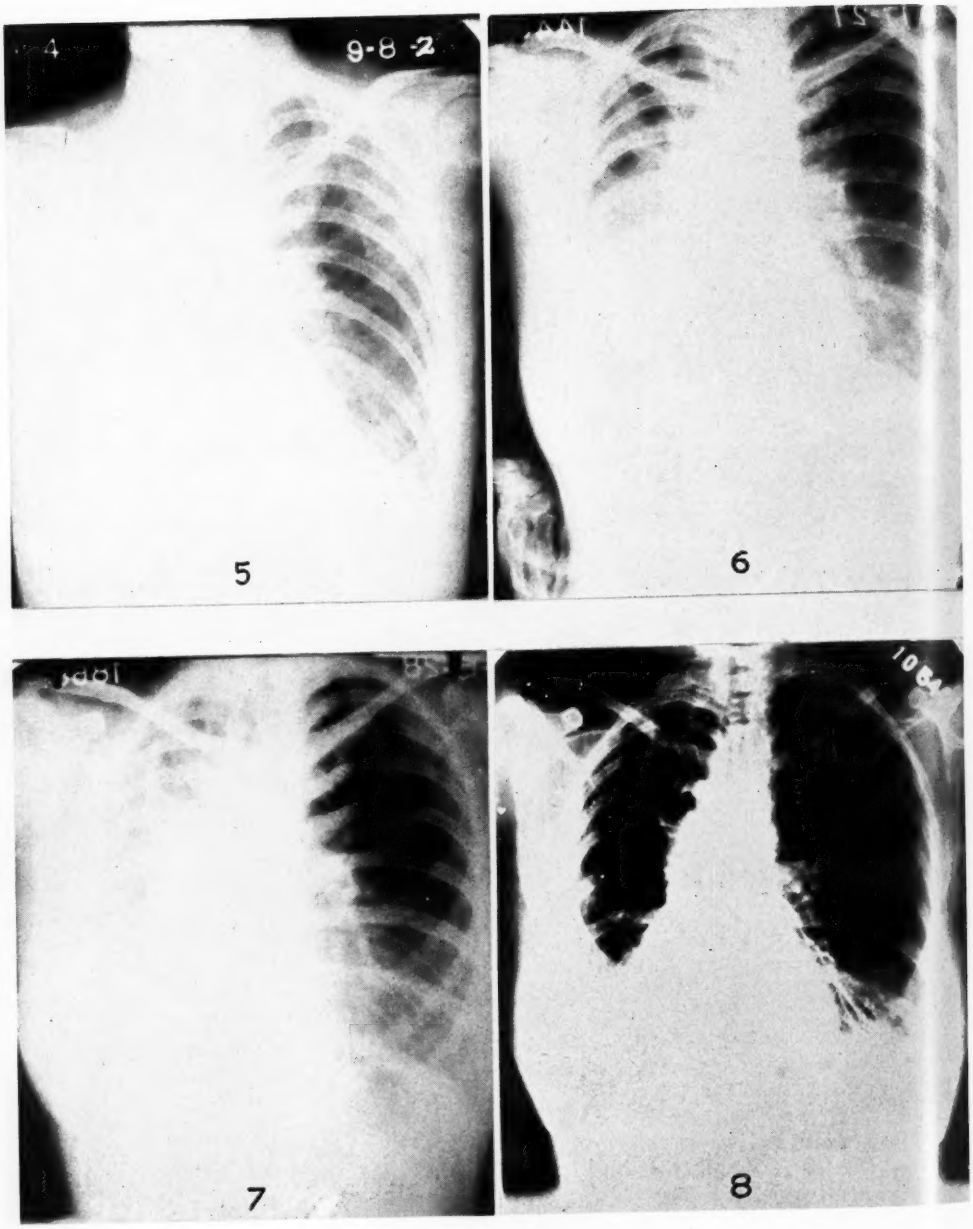
Subsequent Course

When this case-report had been finished, except for a bronchoscopic examination and a possible study of the right lung after an injection of lipiodol, the the patient was transferred to the Diagnostic Centre, U. S. Veterans' Hospital, Palo Alto, California, for these studies.

There a diagnosis was made as follows: "Chronic intermittent stenosis of the right major bronchus, cause unknown, possibly a mediastinal lymphangitis following influenza and possibly some encapsulated mediastino-pleuro-empyema."

The bronchoscopist reported:

> Larynx and trachea normal except that trachea is markedly inclined to the right side. The bifurcation of the trachea showed a wide lip at the entrance of the left main bronchus below which the left main bronchus appeared normal. About one-half of an inch below the bifurcation the right main bronchus was almost entirely occluded by a vascular, nodular, bluish-red tumor mass of granulation tissue. This apparently was attached to the lateral and posterior wall of the right main bronchus just above the usual level of the entrance to the right lobe bronchus. A bougie passed medial and anterior to this mass. *Diagnosis*: Granulation tissue, occluding right major bronchus. The above findings corroborate the diagnosis of chronic intermittent bronchial stenosis, caused probably by lymphadenitis at the hilum with ulceration into the bronchus. Nature of lymphadenitis undetermined, it being deemed inadvisable to remove a specimen on account of previous haemorrhages.



FIGS. 5 TO 8

For description and interpretation see text

SUMMARY

Our hospital records show that there were 18 guinea pigs negative for tubercle, and 23 negative sputum examinations for tubercle bacilli, 18 of which were certified. In view of these facts and the repeated chest and radiological findings, the absence of typical group symptoms of pulmonary tuberculosis and the course of the disease, the staff feels justified in excluding the presence of pulmonary tuberculosis.

In our studies we have considered, as possible aetiological factors or complications, hilum tuberculosis, aneurysm of the arch of the aorta, gumma of the lungs (there were four negative blood Wassermann reactions), fungus growths, foreign body, thickened pleura, localized pneumonia, lung abscess, substernal goitre, and massive pulmonary collapse.

We have based the title of this report on the following facts: The disability was postinfluenzal. Radiological findings have shown at different dates a movable lobulated mass near the upper pole of the right hilum, which probably has caused a characteristic pressure symptom, such as an inconstant "brassy" cough, pain, recurring pneumonic infiltrations with pleural effusions, dyspnoea, and a marked displacement of the mediastinum to the right. The series of haemorrhages independent of the so called pneumonias, as to time, appear to lend weight to the diagnosis of a bronchial sac or cyst, as there was no rise of temperature or acceleration of pulse, or aspiration pneumonia following. That the acute exacerbations in the lung and pleura have occurred in more or less regular cycles, without apparent cause, lead us to the conclusion that, when the cystic mass filled, it overflowed, and the result of this incubated overflow manifested itself as an inflammatory condition of the lung which pursues the clinical course of a lobar pneumonia.

We acknowledge our appreciation for the help Dr. Kennon Dunham has given in the interpretation of this series of radiographs and for the assistance rendered by the staff at the Diagnostic Centre, U. S. Veterans' Hospital, Palo Alto, California.

MULTIPLE PULMONARY ABSCESSES RESULTING FROM BLOOD INFECTION BY MICROÖRGANISMS OF THE PROTEUS GROUP[1]

M. J. KING AND R. H. MORGAN

Bacillus proteus, in the rôle of a pathogenic microörganism producing chronic pulmonary disease with abscess, is sufficiently unusual to warrant reporting this case received at the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

Larson and Bell (1), in a series of animal experiments to determine the pathogenic properties of *Bacillus proteus*, were able to produce lesions. They worked with five strains isolated, respectively, from a laparotomy wound, a postoperative eye infection, an infected finger, the heart's blood of a case of peritonitis following a gunshot wound of the intestines, and a case of gangrene of the lung. These strains were all pathogenic for rabbits, subcutaneous inoculation producing typical abscesses.

B. S. Kline (2) reported a proteus bacillus, highly pathogenic for rabbits, isolated forty-eight hours postmortem from human bone-marrow in a case presenting clinical manifestations of pernicious anaemia.

A number of investigators have recovered proteus either in pure culture or associated with other microörganisms in various pathological conditions. Wenner and Rettger (3), in a review of the literature, refer to many of these studies. They conclude that "while this genus is ordinarily regarded as non-pathogenic, there is ample evidence to show that it may assume a pathogenic rôle and thus occupy a position analagous to the pyogenic micrococci."

Kernan (4) reported two cases of infection by *B. proteus*. In one instance, a case of lateral sinus thrombosis, proteus bacilli were cultured from the blood during life and postmortem from an epidural abscess; in the second, a case of peritonsillar abscess terminating fatally, the only microörganism recovered was *B. proteus*.

Warren and Lamb (5) reported a fatal infection with a microörganism of the proteus group in which positive antemortem blood cultures were obtained. This microörganism was closely allied to *Proteus vulgaris* and was pathogenic for laboratory animals, causing septicaemia and necrosis of the liver, heart-muscle and adrenals.

[1] From the Hegeman Memorial Research Laboratory and the Medical Department of the Metropolitan Life Insurance Company Sanatorium, Mount McGregor, New York.

Clinical History

C. V., white, American, age 36, was admitted to the Sanatorium on January 10, 1925, complaining of cough, expectoration, dyspnoea on exertion, weakness, loss of weight, anorexia and constipation. In childhood he was ill with scarlet fever, measles, mumps and pertussis. In 1914 a frontal sinusitis, necessitating a radical operation, followed a tonsillectomy and adenectomy. During the epidemic of 1918 he had severe influenza with pneumonia. Since his sinus operation he had had frequent colds, "catarrh," shortness of breath, and at times asthmatic seizures. During the past three years there had been cough with expectoration of viscid yellow sputum. The cough was frequently paroxysmal. Occasional chills with fever are recorded. He denied pleurisy or haemoptysis. There was no history of venereal disease. During 1924 he had lost 25 pounds.

Physical examination revealed a pale, pasty, undernourished male, 26 per cent below normal weight. The skin was dry but otherwise negative. The nails were not curved and there was no clubbing of the fingers. There was a scar over the left eye resulting from radical operation for sinusitis. The pharynx, tonsils, teeth and gums were negative. The posterior cervical lymph nodes were palpable. The thyroid was negative. The heart and aorta and palpable vessels were negative. The abdomen was slightly tender in the right lower quadrant. The liver was not enlarged or tender and the kidneys and spleen were not palpable. The right inguinal lymph nodes were palpable. The reflexes were normal. The blood-pressure was 102/78. On admission the temperature was 99°, the pulse 80, and the respirations 18.

Examination of the chest disclosed impaired mobility on both sides, especially the right, with some flattening of the chest at the right base. *Right lung:* The percussion note was impaired to the second rib and the seventh vertebral space; no râles were heard. *Left Lung:* Impaired percussion note was heard to the third rib and seventh vertebral space with bronchovesicular breathing at the apex. A few deep-seated medium râles were heard after cough above and below the clavicle, as well as in the axilla, and below the eighth vertebral space after cough.

The roentgenologist reported in the right lung "a small amount of parenchymatous infiltration at the extreme apex and in the circle of the first rib near the periphery; also a few small patches of parenchymatous infiltration at the base, these being atypical of tuberculosis." In the

left lung there was definite thickening of the trunks to the apex, with definite parenchymatous infiltration to the clavicle and third vertebral space. At the base definite mottling was seen, atypical of tuberculosis.

X-ray of the accessory sinuses showed no abnormal findings. Gastro-intestinal fluoroscopy on admission suggested a probable colitis.

A nose and throat examination disclosed a definite atrophic rhinitis with ozaena. No alveolar abscesses were ascertainable by X-ray. The sputum was repeatedly negative for tubercle bacilli, including one guinea-pig inoculation of a concentrated specimen. The further bacteriological findings are described later in this paper. Catheterized urine cultures and blood cultures were negative. The blood-count on admission showed haemoglobin 80 per cent, erythrocytes 4,900,000, and leucocytes 12,000, with 76 per cent polymorphonuclear neutrophiles, 15 per cent lymphocytes, 7 per cent mononuclears, and 2 per cent eosinophiles. A second count showed 12,000 white cells, with 64 per cent polymorphonuclear neutrophiles, 22 per cent lymphocytes, 12 per cent mononuclears, and 2 per cent eosinophiles. The blood Wassermann was negative, the complement fixation for tuberculosis 3 plus, and the sedimentation of the red blood corpuscles 42 per cent. The temperature curve tended toward subnormal, but the pulse was frequently accelerated during his residence.

Cough with expectoration continued. Because of the purulent character of the sputum and the paroxysmal character of the patient's cough, postural treatment was used with at times satisfactory pulmonary drainage.

Microörganisms of the proteus group were obtained in practically pure culture several times from this foul sputum. An autogenous vaccine was used to determine the hypersensitiveness of the patient to this microörganism. Two and one-quarter hours after the injection of the vaccine the patient had a slight chill. His temperature rose over one degree and remained elevated throughout the day. His arm became sore, and in eight hours an inflammatory zone, 12 cm. in diameter, appeared at the site of injection. Vaccine therapy was tried for three months with only indifferent results.

The progress of the patient was uneventful. Physical signs in the lungs repeatedly showed moisture in the base, most pronounced on the right side. The character of breathing was frequently asthmatic. On July 2, 1925, a severe epistaxis developed, and it could be stopped only temporarily by the use of tampons. The bleeding recurred, and in order

that he might be under closer observation of a rhinologist the patient was removed on July 3 to the Saratoga Springs Hospital under the care of Dr. Thomas J. Goodfellow. The bleeding was successfully controlled, but on the evening of July 4 his temperature rose suddenly to 103°–104° after a severe chill and the patient's condition became critical. A proteus infection of the blood-stream was suspected, but the patient died the following morning before a specimen of blood was obtained.

Autopsy Findings

The necropsy was performed two hours after death. The only findings which are of special interest are those in the lungs and sinuses. Both pleural cavities are free from fluid, but there are numerous firm adhesions at both bases, with a few bands at the right apex.

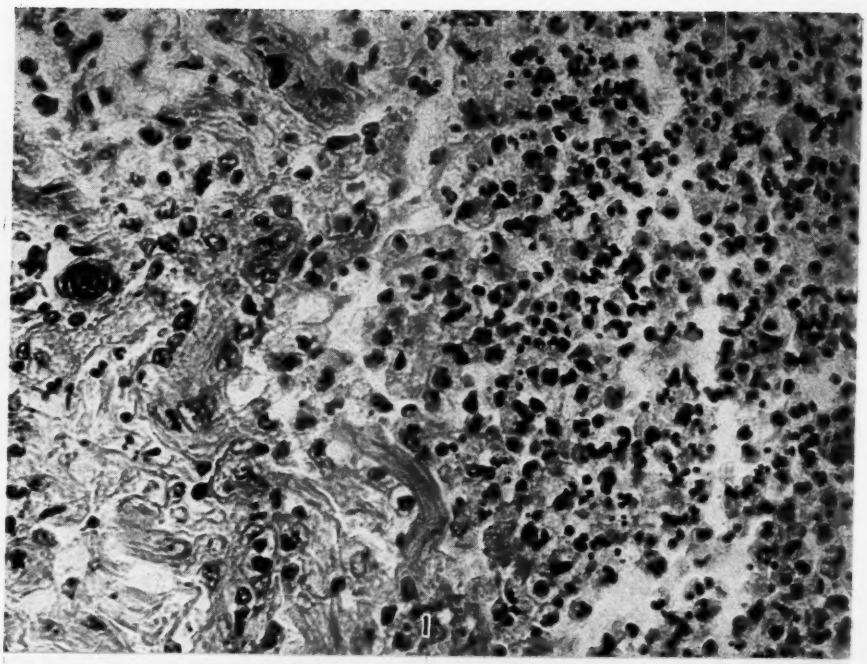
The right lung is nodular on palpation and on section shows foci of congestion and bronchopneumonia. In the upper lobe there are three cherry-sized abscess cavities, each having a distinct wall and connected with a bronchus. A considerable amount of greenish-brown, purulent, foul-smelling material fills these cavities. Cultures of this pus gave microörganisms typical of *Bacillus proteus*. The smaller bronchi leading to the abscesses are dilated and contain greenish-yellow, foul pus. On careful inspection there are several buckshot-sized necrotic foci. The pleura is thickened, and there are numerous whitish bands of tissue running into the lung from it.

The left lung contains no macroscopic abscesses but there are numerous foci of bronchopneumonia.

The left frontal and maxillary sinuses contain thick greenish foul pus from which organisms of the proteus group were cultured.

Anatomical Diagnoses: Bronchopneumonia, bilateral; abscesses of the right lung; chronic interstitial pneumonia, bilateral; chronic purulent bronchitis; chronic fibrous pleuritis, bilateral; chronic purulent sinusitis, left frontal and maxillary; cardiac hypertrophy and dilatation; fatty infiltration of liver; acute congestion of viscera; hypertrophy of prostate; enlarged tracheobronchial and inguinal lymph nodes.

Microscopic Examination: The above anatomical diagnoses are confirmed by histological examination. There is a chronic fibroid pneumonia in both lungs, more extensive in the right, with an increase of connective tissue between the alveoli and around the bronchioles and in the interlobular septa. Scattered throughout this fibrosis is a very marked lymphocytic infiltration simulating lymphoid nodules. The



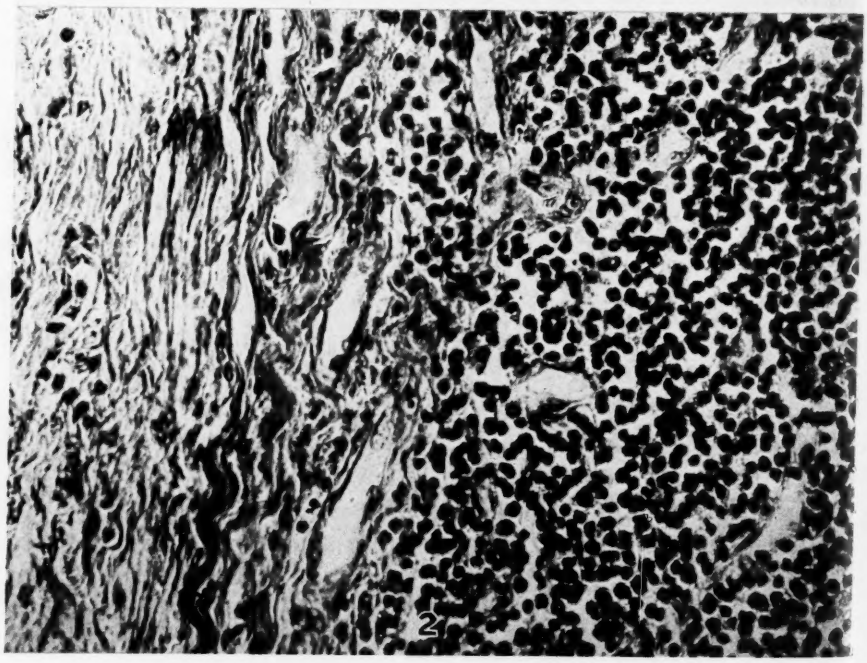


FIG. 1. PORTION OF ABSCESS OF LUNG FROM CASE REPORTED. ×460

FIG. 2. SECTION OF LUNG SHOWING CHRONIC INTERSTITIAL PNEUMONIA. ×470

majority of the cells in the pneumonic exudate in the alveoli are large endothelial cells with reticulated cytoplasm. Phagocytized fat in these cells indicates a chronic rather than an acute pneumonic process. Apparently the larger abscesses in the upper lobe are of long duration. Their walls are composed of dense connective tissue, which is infiltrated by large numbers of lymphocytes. The small abscesses are much more recent in development. The picture in no way suggests tuberculosis and no acid-fast microörganisms can be found in the sections.

Bacteriology

Microörganisms were recovered from three heart's blood cultures, the lung abscesses, and the pus in the frontal and maxillary sinuses, identical with those which were repeatedly cultured from the patient's sputum. They were agglutinated through a dilution of 1–280 in the patient's serum but were not agglutinated in dilutions as low as 1–15 in the sera of ten other patients.

The microörganism is a gram-negative, slightly pleomorphic bacillus, and motile, with peritrichous flagella. It forms no spores or capsule. The optimum temperature is from 25° to 30°C., but it will grow, though more slowly, down to 20°C.

On agar the growth is luxuriant and moist, generally spreading from the bottom of the slant to the top in from 18 to 24 hours, thus differentiating it from *Bacillus zopfi*, *cloacae* and *pseudomonas*. Five per cent gelatine is rather rapidly liquefied. Broth becomes turbid within 24 hours, with slight pellicle-formation in six days. Blood-serum is digested. Litmus milk shows production of slight acidity and coagulation in 24 hours. Peptonization is not complete before twelve days. On Endo's medium the colonies are red and slightly raised, and are both spreading and nonspreading. The fermentations, which are listed in table 1, correspond to the findings of Wenner and Rettger (3) and Bengston (6), and place the microörganism definitely in the proteus group.

TABLE 1

glucose	levulose	galactose	maltose	saccharose	mannite	lactose	dextrin	starch
AG	AG	AG	AG	AG	O	O	O	O

Experimental: The microörganisms were virulent for rabbits and guinea pigs. Septicaemia and early death usually followed the injection

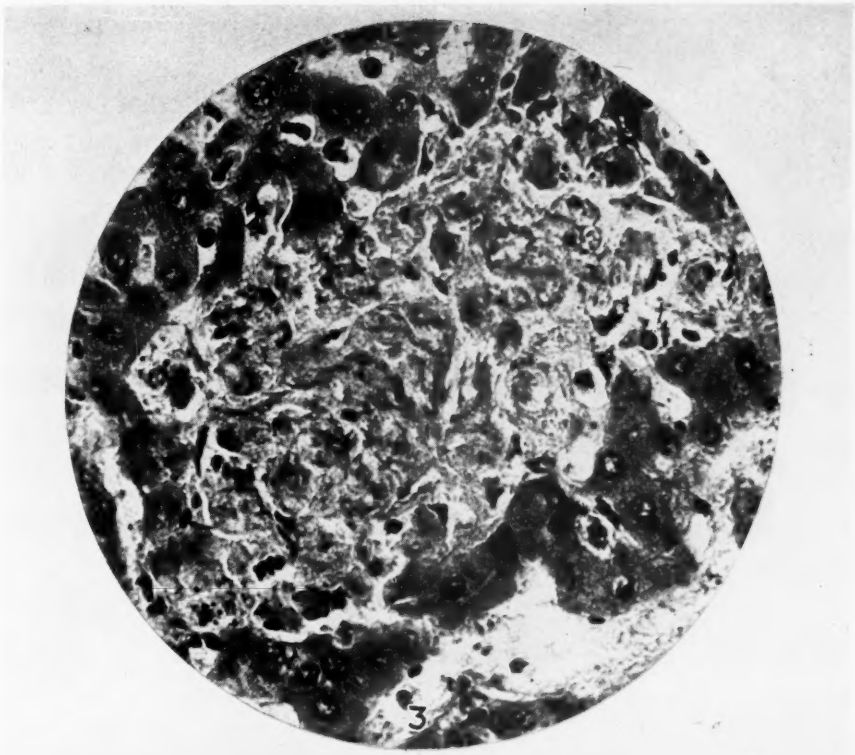
of fairly large doses of living microörganisms. Smaller doses were less likely to cause immediate death, and in a few instances they failed to kill. There was no exact method of determining the extent of reaction in different animals of the same kind. Table 2 gives a brief summary of experimental results in a few of the rabbits used.

TABLE 2

	DOSE	METHOD	DIED	AGGLUTINATION TITRE	CULTURE OF HEART'S BLOOD	PATHOLOGICAL FINDINGS
A	0.2 cc. broth	Intravenous	12 hours	0	Positive	Septicaemia
B	0.3 cc. broth	Intravenous	18 hours	0	Positive	Septicaemia
C	0.2 cc. saline	Intravenous	3 days	1–24,000	Positive	Histological foci of necrosis in liver and heart
D	0.2 cc. saline	Intravenous	4 days	1–800	Negative	Negative; endothelial reaction in spleen
E	0.5 cc. broth	Intraperitoneal	8 days	1–32,000	Positive	Necrosis of liver; spleen enlarged; liver culture positive

Septicaemia nearly always followed the injection of living microörganisms, with liver necrosis in animals which lived at least three days after infection. In some of our animals necrosis occurred in the heart-muscle; this was not produced until some time after the liver necrosis appeared. Salt-solution suspensions of agar-grown bacilli produced the same lesions as were produced by broth cultures. The latter, however, given intravenously, showed a greater tendency to produce symptoms of toxaemia shortly after injection, or early death.

Berkefeld-V filtrates of 18- to 24-hour broth cultures, carefully tested for sterility, produced symptoms similar to those produced when broth cultures were injected. In rabbits, uneasiness, dyspnoea, prostration and death were produced by intravenous injections of from 5 to 10 cc. of the filtrate. As with cultures, the filtrate acted differently in different animals and dosages. Several rabbits were killed with doses of 5 cc. intravenously. One rabbit received 5 cc. by vein every three days for three doses. Four days after the last injection it was killed. Definite foci of necrosis had been produced in the liver and heart. The exact nature of the toxin in this filtrate is uncertain. It may be a true exotoxin or it may be in the nature of the "X" substance of Zinsser (7). It is thermolabile, being completely destroyed in thirty minutes at 56°C.



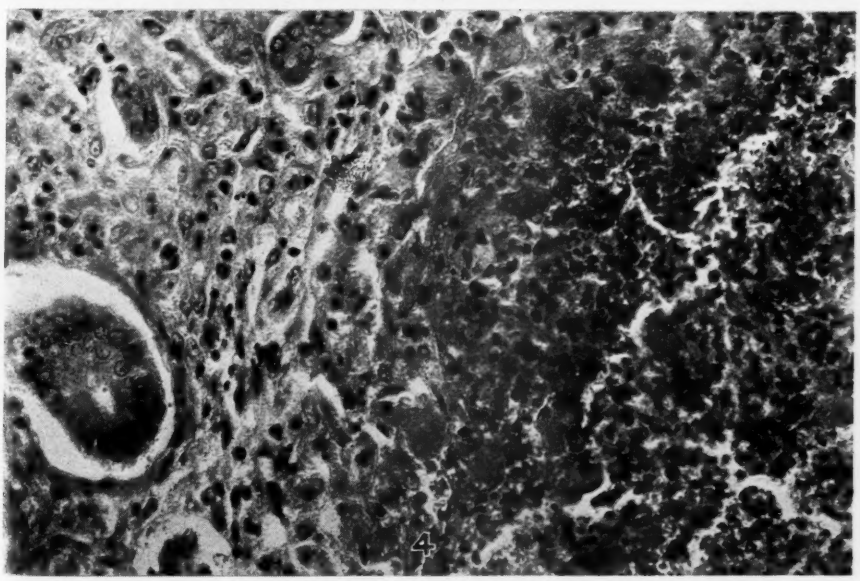


FIG. 3. RABBIT C. SECTION OF LIVER SHOWING SMALL AREA OF FOCAL NECROSIS. ×500

FIG. 4. RABBIT E. SECTION OF LIVER SHOWING ACUTE ABSCESS. ×420

In 1900 Kraus and Clairmont (8) demonstrated an haemotoxin-producing power of *B. proteus*. Kline (2) isolated from human bone-marrow a strain of *B. proteus* which possessed great haemolytic power. Ecker and Brittingham (9) found that this lytic principle was independent of the life of the microörganism, the cultures remaining toxic after cell death. The lytic substance was filterable through a Berkefeld candle. They further found that different strains of *B. proteus* varied in their ability to produce haemotoxins. These authors were unable to demonstrate a haemotoxin with our strain which is designated as "N. Y." in their paper. Wenner and Rettger (3) failed to find any strain of proteus possessing haemolytic power. Braun and Chao Shi-Tsing (10) found no haemotoxic action after Berkefeld filtration or destruction of B. proteus.

SUMMARY

1. Recorded cases of human infection with *B. proteus* are infrequent. A case is presented here in which positive blood-cultures were obtained two hours after death. The microörganisms were also cultured from lung abscesses and from pus in the frontal and maxillary sinuses. *B. proteus* had been repeatedly cultured from the sputum for several months before death.

2. The microörganism isolated is unquestionably of the proteus group and is pathogenic for rabbits and guinea pigs. Necrosis of the liver and heart-muscle is produced in experimental animals.

3. A thermolabile toxin is produced in young broth-cultures which experimentally produced lesions comparable to those produced by living microörganisms.

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BRONCHIECTASIS[1]

HAROLD BRUNN AND WILLIAM B. FAULKNER, JR.[2]

The term *bronchiectasis*, from long association and perhaps from textbook descriptions, brings to the mind of most of us the picture of a hopeless patient, with a pasty, septic look, harassing cough, and copious foul expectoration, and one whose obnoxious breath practically ostracizes him from human association.

Our present-day viewpoint, we will attempt to show, is entirely different. With our modern methods of diagnosis, and especially with the use of lipiodol, we have come to recognize bronchiectatic enlargements as a very chronic disease, beginning frequently in early childhood, with symptoms of only moderate severity extending over many years, and perhaps never reaching the ultimate stage described above, the patient living a long and useful life with only moderate disability. It has, therefore, come to be known as a very common pulmonary condition. Next to tuberculosis Hedblom considers it the most frequent chronic pulmonary disturbance. It will be found in many patients who in the past have been treated for chronic bronchitis, asthma, or even tuberculosis. It may become a part of a tuberculous process or it may be the striking feature of a hidden malignant tumor of the lung. It is not uncommon for the surgeon to open a bronchiectatic abscess and find, on removing tissue from its walls, that he has been dealing with a carcinoma.

With this loosely drawn picture of bronchiectasis in our minds let us consider how it is, and why, the bronchial tree dilates. It is unnecessary before this group to state in detail the many factors which may lead up to this condition. Suffice it to say that many of these are mechanical in nature and may be both intrabronchial and extrabronchial, producing more or less occlusion of the bronchus and thereby permitting the free ingress of air but not its complete expulsion. This may be caused by foreign bodies, tumors, viscid mucous plugs, enlarged lymph nodes, etc. In normal persons we believe these occlusions tend to produce an emphy-

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[2] University of California, San Francisco, California.

sema rather than a dilatation of the bronchus. We would stress the factor of antecedent infection as the important necessary corollary in the production of bronchial dilatation. Infections of the bronchial tree, chronic in nature, with exacerbations throughout the years, causes, first, round-cell infiltration, and later the production of peribronchial fibrous tissue with damage to the walls of the bronchus. These changes set the stage for the ultimate bronchiectatic case.

In looking over our numerous histories we, of course, find varying stories as to the onset of the disease. If careful histories are taken we find, in general, two types. Those cases of rather short duration usually give a history of several severe influenzal attacks. This disease seems particularly capable of creating a weakening of the bronchial wall. The other type, of much longer duration, and of which there is a larger proportion, seems to have its beginning in early childhood.

As an example of the first instance let us quote the history of J. M., age 36, who in 1916 had pneumonia which laid him up for three months. Here was produced the first weakening in the bronchial wall. An influenzal attack in 1918 disabled him for two months. These were the only serious illnesses in his life. Since the influenzal attack he has had a chronic productive cough, with occasional severe pains in the left chest, suggesting pleurisy, and frequently accompanied by mild or severe haemorrhages. In spite of this the patient continued to work, and it was not until February, 1924, six years after his influenzal attack, that he began to cough up large amounts of foul sputum. Here, then, we have the setting of one type which is very common for bronchiectasis. Had a lipiodol injection been made following the patient's pneumonia in 1916 some cylindrical dilatation of his bronchi would probably have been found.

A typical example of the other type is Mrs. I. M., 26 years of age. She gives a history of frequent bronchitic attacks from infancy to the age of eight years. In 1918 a suspension of the uterus and appendicectomy were followed by pneumonia, since when she has had a persistent cough with expectoration. Already as a child there was probably in this case potential bronchiectasis. The operation and the pneumonia following it now bring it to a crisis. It was not until eight months afterward, however, that the woman began to cough up large quantities of foul sputum mixed with blood. When we saw her she was raising 400 to 600 cc. of sputum during the twenty-four hours.

Another case similar in nature is a boy of 22 years of age. Since the

patient had scarlet fever at the age of four he has had a productive cough, always raising mucopurulent sputum, but not foul. Throughout his life he has had to lay off work from time to time, with acute exacerbations, which finally led to a gradually increased amount of sputum, slightly foul, and with large bronchiectatic dilatations. Had this patient had an operation, an attack of pneumonia or influenza, his condition would have no doubt been made very much worse.

This experience has led us to study more and more carefully cases in the children's ward following infectious diseases, especially those complicated with upper respiratory-tract infections, such as measles, whooping-cough and scarlet fever, and those cases coming into the wards with chronic coughs following such diseases. Lipiodol injections in these cases show dilatations of the bronchi and we call them potential cases, some of which will increase in severity because of continued reinfections, or may break into a full-fledged case immediately as the result of some superimposed infection, such as pneumonia, or of a surgical operation. We think that this type of early case frequently has more than one lobe involved; usually one side is more affected than the other, but it is common to find a middle-, upper-, or contralateral-lobe involvement, even though it be to a lesser degree.

No one who deals with these cases of bronchiectasis can fail to recognize the very great importance of associated sinus disease. Very early the attention of the profession was called to this by Mueller, Rist, and Webb, and by many other clinical papers in recent years. We believe it uncommon not to find a sinusitis accompanying bronchiectatic cases, and we believe that, in the type of bronchiectasis which has its beginning in early childhood following infectious diseases, the sinus plays a very considerable part in keeping up the recurrent infections which lead to the final bronchiectatis. We note that in these children much more attention is given to the ear condition than to the condition of the sinuses by the pediatrician. After the ears have been cleaned up the sinus frequently remains as a chronic condition, not obtruding itself diagnostically unless searched for, and these cases go on for years with such a history of sinusitis. In the two cases cited above as beginning in childhood a marked double sinusitis was found, and we have no doubt that it was present from childhood; and it will occur to you, as it does to us, that very frequently changes in climate, which are so apt to affect sinus trouble favorably, play a considerable part in the improvement which takes place in the pulmonary condition.

It has been our experience in a few instances in which operation seemed justifiable, to find, upon carrying out hygienic and drainage methods along with a thorough cleaning up of the sinuses, that the bronchiectatic condition immediately changed from a rather severe to a very mild disorder, which made us hesitate to offer any surgical procedure for its cure. We feel, therefore, that the incidence of bronchiectasis might be diminished in its inception in a certain proportion of cases by the early recognition and treatment of sinus troubles in early life, following the infectious diseases of childhood.

This, then, in a crude way is the picture of bronchiectasis, that we have in our minds. Let us say a word further concerning the frequent use in the last few years, especially by surgeons, of the term *Chronic Lung Suppurations*, which is made to include not only true bronchiectasis but other forms of pulmonary suppurations as well. This grouping of diseases under one term has, we think, no real advantage. From our own experience we feel that these multiple chronic suppurative processes have for the most part a different beginning. The parenchyma rather than the bronchi is the seat of the disease, which extends or breaks into the bronchus rather than from it. We believe that these cases run a somewhat different course, with more frequent and rather more severe acute exacerbations; that with lipiodol they do not fill as readily nor in the same way as do true bronchiectatic cases; and that frequently there are abscesses in the surrounding lung, which are not shown in the X-ray and which have not as yet broken into a bronchus. It is our opinion that these multiple abscesses of the honeycomb type should not be classified with the true bronchiectatic case and are probably not suited to the same operative procedure. We believe, therefore, that, both pathologically and clinically and from the standpoint of treatment, they are different entities; and it should be our endeavor, as far as possible, to discriminate between these different pathological processes rather than to group them under one general heading, since they have so many distinguishing features.

In the study of a case of bronchiectasis a number of procedures are carried out. The use of lipiodol is of course virtually essential, not only for the diagnosis of the disease, but because it also gives us, as never before, the extent of the disease and the number of lobes involved, and tells us whether it is bilateral, and on which side the disease is most extensive, all of which points are most important in the decision as to treatment.

The use of the bronchoscope is an invaluable aid in determining the

presence or absence of a foreign body, a tumor, or stenosis of the bronchus, and for diagnostic cultures directly from the bronchial tree. Every case, therefore, should have a diagnostic bronchoscope, and it may be continued as a method of treatment, either in itself or as preliminary to operation, in order to obtain better drainage and clear up surrounding parenchymal infections. We ourselves believe that bronchoscopy has its greatest advantage through suction drainage, the emptying of cavitations, the removal of plugs and granulations, etc., rather than through any medication that may be put into the bronchial tree.

Artificial pneumothorax has the advantage of informing us whether or not there are dense adhesions around the lung. This will perhaps give us a clue as to the type of operation which may be best suited to the case. The introduction of air into the pleural cavity has also been used as a method of treatment in certain clinics. It is our belief, however, that this measure alone will never receive the wide acceptance that it has had in tuberculosis, since in tuberculosis rest is the main consideration, while in this infectious process drainage is the main problem, and the use of pneumothorax may prevent rather than facilitate it and thereby lead to an extension rather than improvement of the disease. Even though some very remarkable results have been obtained by pneumothorax therapy we believe that it should be used with a great deal of care as a form of treatment, but as a diagnostic aid it has advantages in giving added information.

Phrenectomy we have not used, and would not recommend it as a cure in itself, but it may be useful as a subsidiary measure to an operative procedure.

The cure of these long-suffering patients has been the aim and despair of surgeons for years. It is evident, however, that, with a picture so varied and with diagnosis possible so early, no one form of treatment will be suggested for every case. While it has been said that bronchiectasis cannot be cured medically it does not follow that every case of bronchiectasis is a surgical problem. He would indeed be a very brave surgeon, not to say a dangerous one, who would recommend operation for every case of bronchiectasis that he encounters. It will be seen that we have to deal with this disease in every stage of its long development, and that even in its early stages there may be multiple lesions in different lobes, so that an absolute cure by any procedure may be too much to expect.

In this discussion we do not wish to lead anyone to suppose that surgery should be adopted only as a last resort. It has for years been the

contention of surgeons that these cases have been brought to them in practically only a hopeless condition. We believe, however, that a decision can be reached many times early in the course of the disease when it is evident that there can be no prospect of otherwise ameliorating the condition to any extent or with permanence by the usual methods of treatment.

A great deal of thought and consideration must be given to the choice of case to be subjected to surgical interference, and it is not an easy matter to put down any definite rule of surgical indications.

Preliminary treatment is essential with most patients before any operative procedure is undertaken. This consists of rest in bed, sunlight, postural drainage, the use of the bronchoscope, cleaning up of the sinuses, and possibly the use of vaccines, and in cases of spirochaetal infections the use of neosalvarsan. Such treatment may occupy from two to six months. We aim to have little or no parenchymatous involvement of the surrounding lung and no temperature reaction. By these measures we increase the vital capacity and the resistance of the patient before operation is undertaken.

Of the operative procedures a number have been devised for the cure of bronchiectasis. The efforts made along these lines in different clinics show how unsatisfactory, to date, have been the results of surgery in the hands of even the best thoracic operators.

We will first speak of the graded extrapleural thoracoplasty of Hedblom. This operation is performed under local and combined anaesthesia in stages, their number depending upon the condition of the patient. In a series of 14 cases Hedblom has had no mortality, and, although the diseased bronchi are not eradicated, the operation in his hands has proved effective "to the extent of markedly relieving cough and sputum in all cases and approximating a cure in many." Hedblom however states that the operation should be done only for cases of uncomplicated bronchiectasis without parenchymal abscesses or pneumonitis. In cases with multiple or multilocular parenchymal abscesses he states that this operation is relatively ineffective and the postoperative mortality high, —approximately 40 per cent.

The cautery pneumonectomy of Graham is recommended by him for the refractory chronic cases representing bad surgical risks. Graham first makes an extensive exposure of the portion of the lung involved by the removal of three to four ribs for the distance of four inches each. Then without separating adhesions, but, on the contrary, establishing

them if none already exist, a large area is cauterized with the actual cautery. The idea is to establish numerous bronchial fistulae, through which massive drainage may be accomplished. At later stages more and more lung is burned away until the disease has been eradicated. Graham reports, in all, 45 cases with 3 deaths. In 31 of the cases, or 69 per cent, there is freedom from symptoms. Considering the serious type of case, this makes a very remarkable showing.

Whittemore recently reported a small series of cases with very good results, which is an improvement on the suggestion of Lockwood. It may be called "exteriorization" of the lung. A considerable number of ribs are removed over the lower lobe. The diseased lobe is freed from adhesions and brought out of the chest-wall. The removal of the ribs is necessary in order to depress the chest-wall around the pedicle of the lung. The lung is sewed to the surrounding muscles, and packing is placed so that the lung is now extrapleural and lies outside the thoracic cavity. This is allowed to slough away or is gradually burned away with the cautery. This operation also has limitations in that the lobe may be very adherent and not easily mobilized, so that it cannot be brought well outside the thoracic cavity. There may also be difficulty in mobilizing at the same time the middle lobe, if diseased, and the upper lobe would seem to be quite out of the question. Whittemore reports 4 cases, one a boy of fifteen with an easy convalescence; the second case, aged nineteen, was not so successful, still having sputum and a bronchial fistula; the third case, forty-six years of age, was very successful; and the fourth case, a patient aged twelve, died as a result of pneumonia on the opposite side. This operation has advantages that will no doubt lead to its further use. It may be used as an alternative procedure to lobectomy should it suddenly become necessary to bring the operation to a close. The lung may be brought out externally by this method. One possible disadvantage might be mentioned. This is that the mobilization and handling of the lung and the necessary manipulation to fasten it to the chest-wall, the pedicle not being clamped, open the way to embolic death. Indeed, it may well be that Whittemore's last case that died of pneumonia of the opposite side was embolic in nature.

The operation of lobectomy, that is, the removal of one or more diseased lobes for bronchiectasis, must appeal to everyone as the ultimate goal in thoracic surgery. It removes at one stroke the diseased lung, it diminishes the period of convalescence, it is not deforming and it more nearly conforms to the procedures we are accustomed to apply for dis-

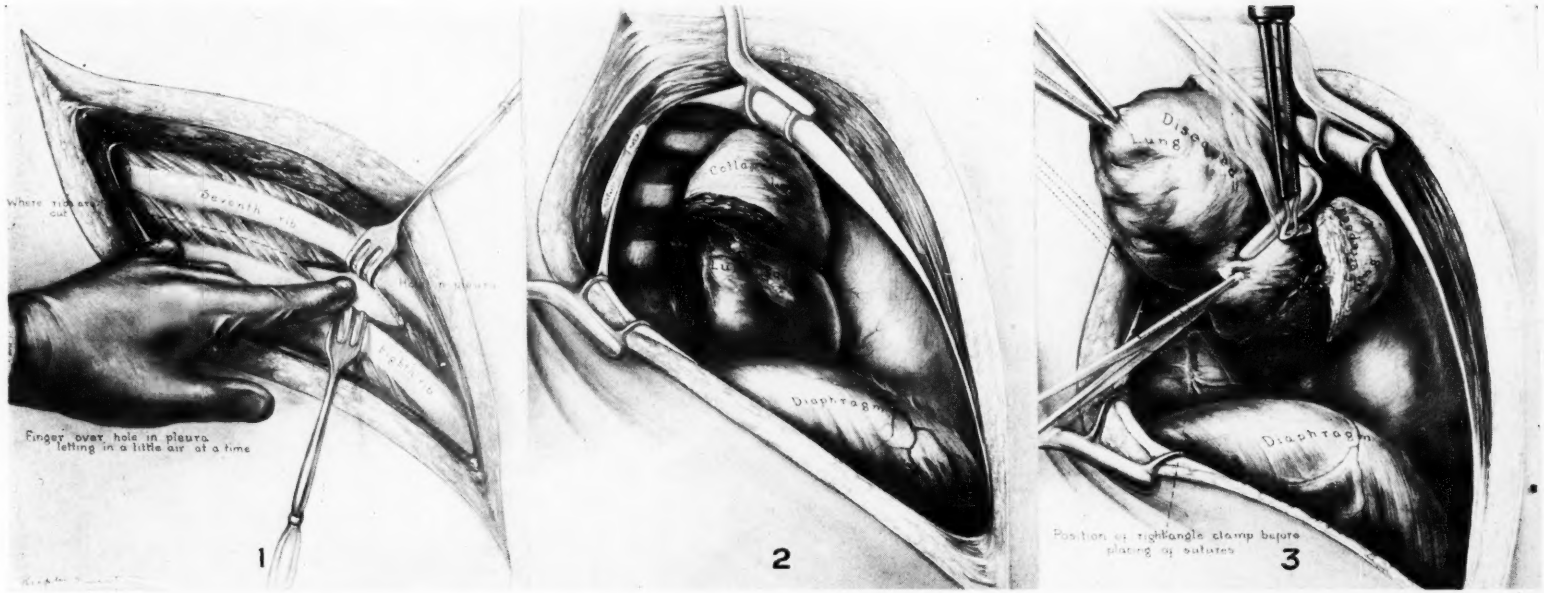
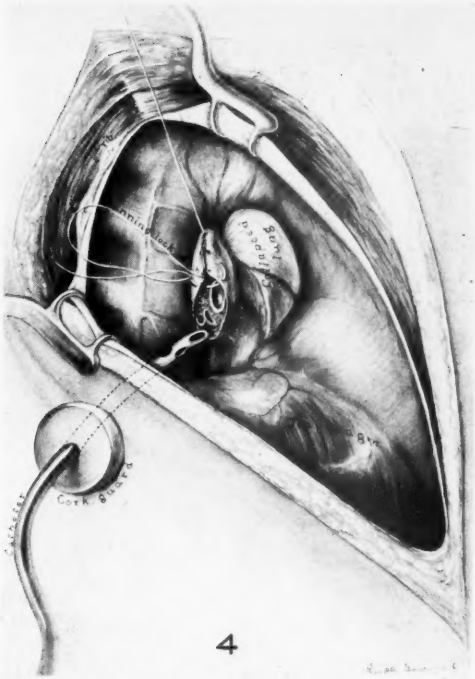


FIG. 1. A long intercostal incision between the 7th and 8th ribs extending from the cartilages anteriorly to the costal angle. The dotted line shows where the ribs are severed posteriorly. A small nick has been made in the pleura over which the finger has been placed in order to permit the air to enter slowly and allow gradual collapse of the lung.

FIG. 2. The ribs have been retracted with the Balfour retractor. Severed ribs shown posteriorly and working field developed. The upper lobes above are collapsed and the diseased lung somewhat thickened. Adhesions to the diaphragm and between the lobes have been separated to develop the pedicle.

FIG. 3. The pedicle has been clamped at the base and double interlocking chromic-gut sutures tied. The cautery is cutting below the distal clamps, leaving a liberal stump behind the ligatures.



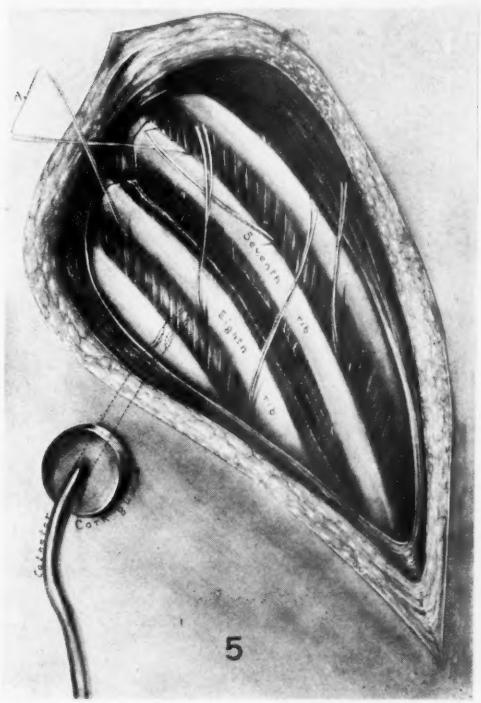


FIG. 4. The pedicle is being closed over with a running stitch of chromic gut. A drainage tube has been inserted through the intercostal space below, extending a short distance into the pleural cavity and guarded by a cork to prevent leakage of air.

FIG. 5. Method of wound closure. Ribs being brought together. Muscles sewed in layers. Air-tight wound.

eases in other organs of the body. Just as cholecystectomy superseded cholecystotomy, and as hysterectomy superseded the old-time method of extraperitoneal treatment of the uterine stump for fibroids, may we not also expect in the future that lobectomy will be the operation of choice in many cases of bronchiectasis?

Lobectomy has been carried out by Lilienthal more frequently than by any other surgeon in America, and among the reasons for its slow acceptance has been its high mortality, which in many clinics was considered prohibitive. Lilienthal cites a mortality of 47 per cent in his book. Whittemore, with six operations for lobectomy, had 100 per cent mortality. However, he admits to considerable ill luck. One case had an uneventful convalescence but died on the sixteenth day from a sudden haemorrhage. One case died after a transfusion, and Whittemore felt that the transfusion had a good deal to do with *exitus*. Still another died three or four days after operation with cause undetermined, and another case died of shock. This, at best, is not a mortality which would lead one to further experimentation.

We have always been very much interested in the operation of lobectomy and have followed the steps outlined by Lilienthal, and modified from time to time as experience seemed to direct. We have had 5 cases of bronchiectasis with one death due to a haemorrhage, which was probably preventable, and have recently removed the lower and middle lobes of a very interesting case which proved, however, to be a carcinoma of the lung. Convalescence was easy, and the patient made a remarkable operative recovery, getting out of bed in two weeks.

Our technique has changed from case to case, and the number also has been so small that one can draw no definite conclusions from this small series. Nevertheless we feel that when we have been able to carry out the procedure in all its details we are confident of a convalescence that is easy and accompanied with very little shock.

Our present operation can in a general way be seen in the accompanying illustrations. The procedure was fully described at the last meeting of the American Association for Thoracic Surgery in Washington and will appear in the January *Archives of Surgery*.

TUBERCULOUS ULCERATION OF THE BRONCHUS

IN A CASE OF LUNG ABSCESS FOLLOWING TONSILLECTOMY

M. C. MYERSON

For two reasons the observation of an active tuberculous lesion in the bronchus is extremely rare. First, as Jackson (1) has pointed out, only a few cases of tuberculosis of the lung justify bronchoscopy. Second, although lesions of the bronchial tree are not uncommon in tuberculosis, involvement of those branches accessible to bronchoscopy is rather infrequent. What is known about tuberculous infection of the bronchial tree is principally the result of observations at the autopsy table.

The best description of tuberculosis of the bronchus which I have been able to find is that given by Ziegler (2). The following is quoted from his textbook:

> Tuberculous inflammation of the bronchi is a common accompaniment of pulmonary tuberculosis. It is most marked in the smaller tubes immediately connected with the diseased area, but in some cases it is diffused over the greater part of the bronchial system. Here as elsewhere the infection begins as gray cellular nodules which project somewhat above the surface. These caseate and break down, and in this way small ulcers are formed whose floor and edges are surrounded by a hyperemic zone. As the disintegration of the infiltrated margins of the ulcers advances, and the ulcer grows larger and coalesces with others, large and irregular shaped erosions are at length formed which sometimes extend to the cartilage of the bronchial wall. In the smaller tubes we find the entire wall thus invaded and ulcerated away.

In the case about to be reported, extensive involvement of the lower trachea and the right main bronchus, from the upper-lobe branch down to the visible branches of the lower lobe, was encountered in the course of bronchoscopy for drainage and irrigation of a suppurating focus in the upper lobe.

Case Report

A girl of nineteen was referred to the Medical Service of Mount Sinai Hospital by Dr. Yankauer, who saw her three months after the onset of her illness. A

tonsillectomy had been performed under general anaesthesia in September, 1926. One week after the operation she began to cough, had a rise of temperature, and suffered a severe chill. The cough was productive of foul-smelling expectoration. She was bronchoscoped one week after the onset of her symptoms and felt considerably relieved. After this she went to the country for three weeks and returned symptom-free. Shortly after her return, however, she began to cough again and to expectorate a foul greenish-yellow sputum which was rather profuse. It was at this time that she was referred to the hospital.

Physical examination revealed dulness in the right suprascapular and right apical and infraclavicular regions. Râles of a clicking character were to be heard in this region at the end of inspiration. There was increased tactile and vocal fremitus in the right infraclavicular region. At this time the blood-pressure was 110/70. The leucocytes numbered 11,400, there were 76 per cent polymorphonuclears, and the haemoglobin was 70 per cent. The sputum was negative for tubercle bacilli on several occasions. Interpretation of an X-ray film by Dr. Wessler at this time was to the effect that there was an infiltration of the right upper lobe extending from the apex to the second rib anteriorly. He expressed the opinion that this was probably a more or less chronic tuberculous process. After ten days in the hospital the girl was discharged and advised to return regularly for bronchoscopic treatment.

She was readmitted the following May and stayed in the hospital for two months. She had been receiving bronchoscopic aspiration and irrigation in the interim. She returned because her symptoms had become aggravated. At this time X-ray study revealed a marked increase in the size of the involved area of the upper lobe and a pneumonic infiltration of the lower lobe of the right side. At this time, also, there were found numerous acid-fast bacilli which were nodular and in chains. Dr. Schwartzmann, the bacteriologist, did not consider these tubercle bacilli. As a result of bronchoscopy and sunlight the patient was markedly improved. The X-ray study showed an almost complete resolution of the pneumonic process, with a few infiltrations at the right apex and base. (Figure 1. Earlier roentgenographs not available.) The patient was discharged from the hospital.

However, within a month, she returned to the hospital because she felt much worse. She had been coughing almost constantly and expectorating a great deal. Her expectoration, though no longer foul, was quite profuse. On the night before admission she had been unable to cough, she had had a chill and had become dyspnoeic, and she had suffered pain in the right chest. She had also recently suffered a profuse haemoptysis. *Physical examination* revealed increased tactile fremitus over the right lung anteriorly and posteriorly. Dulness was elicited in the second and third spaces anteriorly and also along the inner border of the scapula. Numerous bubbling râles were heard anteriorly

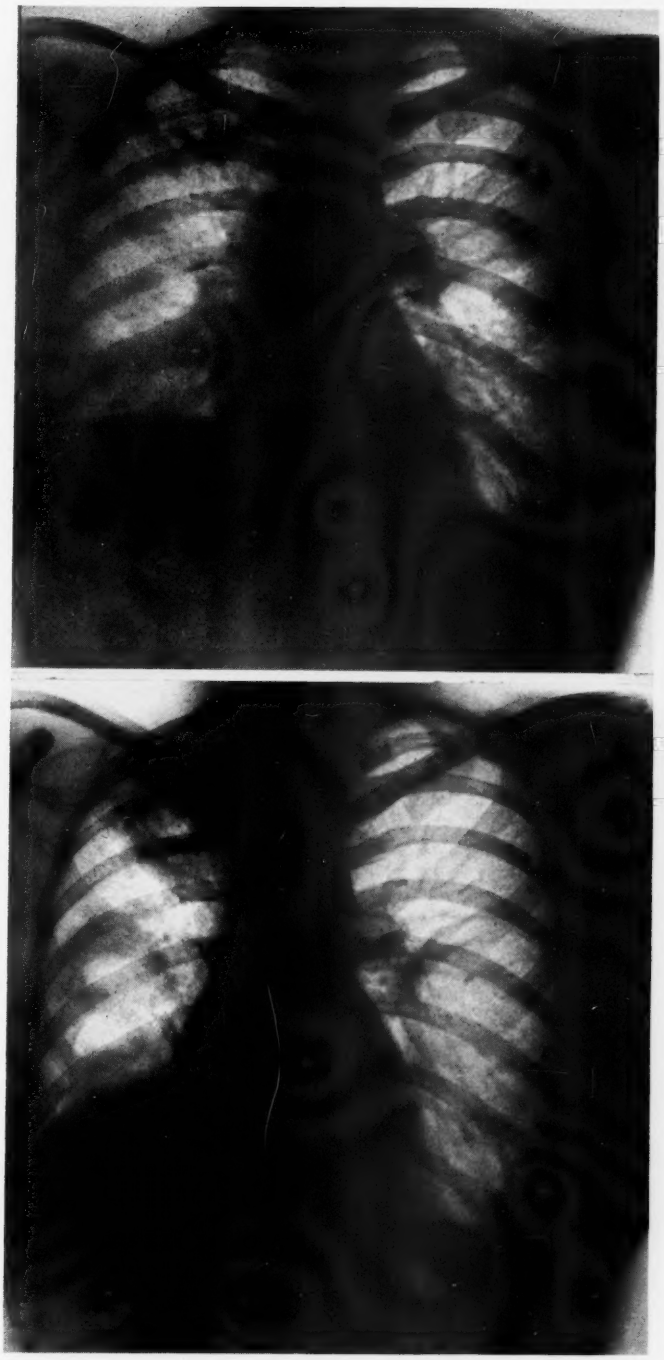


FIG. 1. ROENTGENOGRAPH TAKEN IN SEVENTH MONTH OF ILLNESS
FIG. 2. ROENTGENOGRAPH FOUR MONTHS AFTER FIG. 1

in the second, third and fourth interspaces combined with harsh breathing of the vesicular type. The leucocyte count at this time was 26,200, of which 86 per cent were polymorphonuclears. The haemoglobin was 70 per cent, and the blood-pressure 104/40. The left lung was apparently clear, but the signs

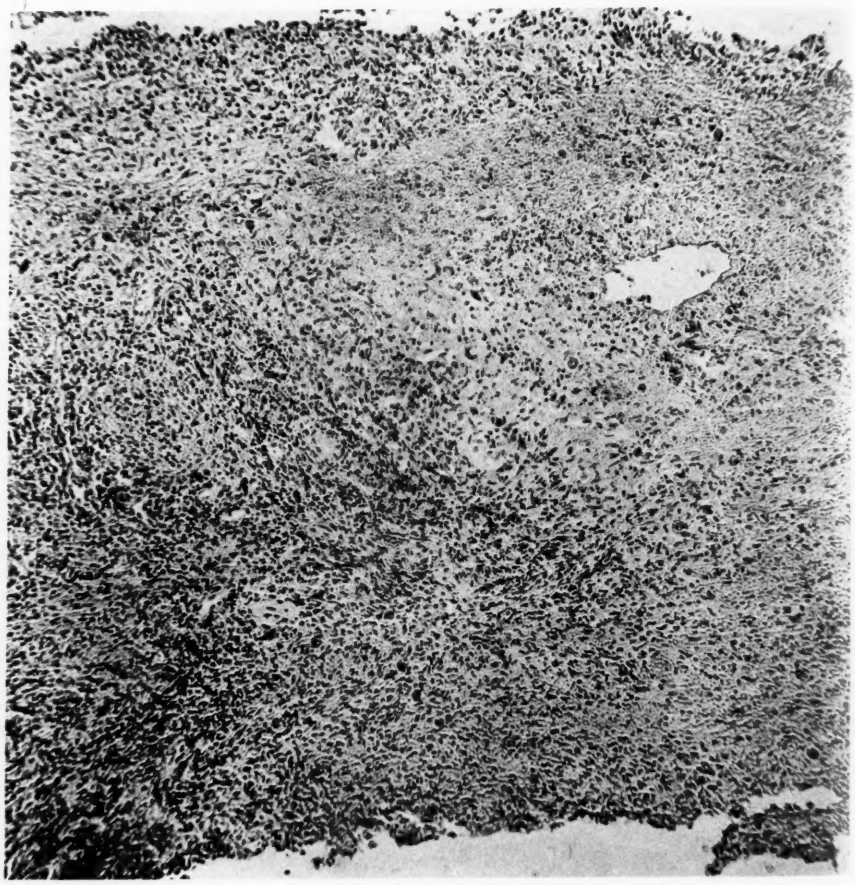


FIG. 3. PHOTOMICROGRAPH (LOW POWER) OF TISSUE REMOVED FROM BRONCHUS, SHOWING TUBERCLE-FORMATION

in the right lower lobe had apparently increased, and here X-ray study early in September had revealed two cavities. The temperature ranged between 99° and 104°, and the pulse rate between 90 and 140. The Wassermann blood test was negative. The sputum continued negative for tubercle bacilli. At this time the patient was seen by Dr. Neuhof who advised surgical drainage. (Figure 2.)

On November 11 she was referred for bronchoscopy. She had not been bronchoscoped for the past three months. At bronchoscopy I found the following:

The mucosa of the tracheal bifurcation was swollen and irregularly granular in appearance. The entire right main bronchus showed a similar appearance. The mucosa appeared to be the site of irregularly elevated granulations and ulcerations of minute size. There was a small amount of exudate which could be wiped off readily. The mucosa bled readily but not profusely. A smear was taken and a specimen removed. The writer was impressed by the unusual picture which presented itself, and could not diagnose the local condition. But, after the smear and the tissue removed were reported upon, the similarity of the bronchial lesion to those lesions of the nasal and oral mucous membrane in tuberculosis was at once apparent. (Figure 3.)

COMMENT

It would be well to consider the possibility of a tuberculous basis or of a superimposed tuberculosis in any case of lung suppuration. This was emphasized by Imperatori's report (3) of several cases of pulmonary suppuration which were found to have a tuberculous basis at autopsy.

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DIAPHRAGMATIC STUDIES IN TUBERCULOSIS[1]

PAUL D. CRIMM

In pulmonary tuberculosis the thoracic physical findings are exceptionally individualistic. A cross-section of such findings presents us with conclusions based on the phenomena of physics, but if we overwork a pet theory or advocate certain physical findings as constant, the X-ray, the fluoroscope and the autopsy stand ever-ready to remind us that the observations were incorrect.

In view of the fact that the X-ray and fluoroscope are not always available, or, when available, the patient's condition does not warrant their utilization, we should have at our command fairly dependable physical findings that are known to reveal the underlying pathological changes of the lungs. Insufficient emphasis is placed on the musculature of the thorax as a valuable aid in the verification of other findings. More important than the tone of the muscles is their method of functioning, whether it be synergistic or antagonistic in normal or abnormal conditions. A routine study of the respiratory muscles not only assists in the earliest possible diagnosis of the pulmonary lesions, but in the end it may hasten surgical procedure before it is too late. In either consideration, the diaphragm plays the leading rôle, as it does in the subsequent observations.

As one of the most important muscles involved in the act of respiration, the diaphragm alone increases the longitudinal diameter of the thorax. In conjunction with the excursion of the ribs, the excursion of the diaphragm creates the negative barometric pressure of the pleural cavity. Clinically, evidence of the excursion of the diaphragm is seen when the abdomen moves during respiration, and if we palpate singly the right and left epigastrium during inspiration we can sometimes ascertain whether the right or left leaflet of the diaphragm is functioning with greater or lesser force in its downward excursion.

Williams studied the inspiratory descent of the diaphragm in tuberculosis under the fluoroscope, and found that, even when disease is confined

[1] From the Connecticut State Tuberculosis Sanatorium, Cedarcrest, Hartford.

to a limited area in one apex, the diaphragm on the affected side shows a diminished inspiratory descent. Findings in this series show this to be true in the majority of cases, but it has many exceptions. Furthermore Williams's *early diaphragmatic sign*, as it is known, requires a fluoroscope, which is not always at hand or practical for the patient requiring absolute bed-rest. Litten's phenomenon, present normally or pathologically, is supposed to show the diaphragm contracting and peeling itself from the chest-wall, but it is so often not demonstrable, except on a patient with a thin and emaciated thorax, that its greatest use lies in occupying a few paragraphs in the textbooks.

Duchenne (1) experimented with the action of the diaphragm, but most of his conclusions were proved to be inaccurate in 1913 by Hoover (2), who was the first to give the correct conception of the respective functions of the muscles of respiration. Hoover proved in the laboratory and in the clinic that the intercostal muscles and the diaphragm are antagonistic, that normally the control is in favor of the intercostals, and that the costal margins indicate the resultant of the two forces which are evidenced in the direction and the degree of the excursion of the costal margin. He further proved that the movement of the costal borders is a reliable index of the elevation and depression of the arch of the diaphragm.

Accordingly, we are not concerned here with evidences of excursion of either the diaphragm or the ribs, but with evidences of the underlying pulmonary changes as interpreted by the activation of the intercostal muscles and the activation of the arch of the diaphragm, through the medium of the costal borders. Since these muscles are antagonists, one cannot study satisfactorily the diaphragm alone clinically unless the costal borders are examined with the aid of palpation.

Heretofore the costal-border phenomenon has been used in the differential diagnosis of pulmonary conditions from such complications as pleurisy, fluid, air, pus, in subdiaphragmatic abscess, in paralysis of the respiratory muscles, in pericardial effusions, and in determining the enlargement of the right or left ventricle of the heart, but no special attempt has been made to find out whether the costal-margin phenomenon might still be a valuable aid in diagnosing those pathological conditions in which the pulmonic tissue and often the diaphragm itself are either infiltrated or attached to the lung, as in malignant tumor, lung abscess, pneumonokoniosis, and tuberculosis,—not to prove that it is tuberculo-

sis, but to verify that pathological change is affecting the extensibility of one or both lungs.

Pleuritic pain during inspiration inhibits the excursion of the intercostals and diaphragm. If it is present, even though pleuritis is not audible by means of the friction rub, the costal margin will be restricted. When pleurisy of the lower lobes is obsolete, although the patient or operator of the stethoscope may not be aware of it, the costal margin generally indicates it with a retarded outward flare. This is especially true if the adhesions extend from the lung to the chest-wall. If the adhesions extend from the lung down to the diaphragm, thereby tenting it, increasing its convexity, and lessening its mechanical advantage, the outward flare is often exaggerated.

In this series physical examinations of the costal margins have been performed in 100 cases and the direction and character of movement noted in each case. Ignoring the physical findings, the X-rays of the 100 cases were read and the findings noted. In addition, each patient was fluoroscoped. Each separate finding was then correlated. None were studied that had acute pain, as this would interfere with the best possible movement. Nor were many listed that were complicated with asthma or emphysema, or enlargement of the heart, as these conditions alone alter the arch of the diaphragm.

Of 20 cases classified as minimal, seventeen showed disparity in the outward movement of the costal margin. Of the seventeen, the normal side of sixteen moved out without restriction, while the abnormal side showed diminished movement of its costal margin from the median line. The one case in which the costal margin of the involved side moved out more than on the normal side was due to the tenting of the respective diaphragm by diaphragmatic adhesions. The three cases of the twenty not showing any disparity, or disparity that would be questionable on account of its slight discernibility, had aged lesions which were scattered and not conglomerate.

Of 34 cases, classified moderately advanced, all except one showed disparity in the flare of the costal margin. One case, in which the flare was equal, had lesions that were contiguous with one hilum but which had not apparently altered the extensibility of the lung, in so far as the eye could detect. In 31 cases the costal margin of the lung not involved, or lesser involved with infiltration, moved further from the midline, or at times was less retarding in its movement, or both, than the costal margin whose corresponding lung was involved or was

more densely involved. In 2 cases in which the costal margin moved further away from the midline with the respective lung more densely involved than the opposite lung, the movement was found to be exaggerated by a tenting of the diaphragm, which diminished its power in favor of the intercostals.

In proving that deactivation of the intercostal muscles occurs, there were three moderately advanced cases that did not show by X-ray and fluoroscope any abnormality in either the contour, the initiation of movement, or the excursion of the diaphragm. These three showed diminished movement of the costal margin on the diseased side, and one would judge that little if any inflammatory disease was present in the diaphragm, that the phrenic nerve was not affected along its course by the disease, and that the infiltration had not greatly diminished the longitudinal extensibility of the lung as it had diminished the transverse and anteroposterior extensibility as expressed by deactivation of the intercostal muscles.

Of 41 cases classified as far-advanced tuberculosis, 3 cases of unilateral lung abscess, and 2 cases of pneumonokoniosis complicated with tuberculosis, all showed a disparity of the costal margin except 2 cases of tuberculosis. In other words, one margin was stationary or else moved away from the midline to a greater or lesser extent than the other costal margin. The two that showed no disparity moved out equally, but they lacked the freedom of motion that the normal costal margin exhibited. One case was bilaterally infiltrated throughout. The other had extensive infiltration throughout the left lung and one-half the right. But the extensively infiltrated lung had a diaphragm that was tented by adhesions, which gave less resistance to the intercostal pull and made the two margins move out equally. The two sides pulling the same, the different amounts of infiltration might further prove that the underlying infiltration of the lung diminishes the activity of the intercostal muscles, no matter in what part of the lung, and that the diaphragm need not be implicated to decrease the outward flare. Three of the far-advanced cases were complicated with emphysema and one had bronchiolar hypertonus. Of the 41 cases, thirty-six showed a disparity of the lesser flare on the side most involved.

Thirteen cases showed definite tenting of the diaphragm, while twenty-four gave evidence of lateral adhesions about the lower lobes. In several cases with lateral adhesions, that is, adhesions between lungs and ribs, earlier X-rays demonstrated the bands of tissue while later ones did not

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(density of film remaining the same). However, Hoover's costal-margin phenomenon remained constant. Two in a series of artificial-pneumothorax cases showed, extremely well, tenting of the diaphragm on the one side, and upon the institution of pneumothorax the diaphragm was elevated by the adhesions between it and the lung. Whether the pneumothorax be spontaneous or artificial, with the thoracic cavity completely filled with air, the bands of diaphragmatic adhesions, if they did not break, would cause an outward flare of the costal margin. Ordinarily the margin's flare would vary with the quantity of air or fluid, as the case may be. One case developed fluid in quantity sufficient to render the margin stationary, yet the outward flare continued because of the diaphragmatic adhesions. Diaphragmatic adhesions are more favorable to, say, a phrenicectomy, than a pnemothorax, yet favorable results are obtained with the latter because of upward compression of the entire lung.

Seven cases at autopsy showed diaphragmatic adhesions to be isolated bands or in groups of two and four, except one case that had a far-advanced anthracosis and minimal tuberculosis. Here the left lower lobe was plastered to the diaphragm with fine adhesions, and lateral adhesions in various areas were as numerous in both lungs as in some cases of tuberculosis with multiple cavitations. The diaphragm itself was not grossly involved except in one case, in which the left leaflet contained one calcified tubercle. However, Landis (3) studied microscopically the diaphragm in 9 cases of tuberculosis, and all of them showed the presence of miliary and conglomerate tubercles.

Displacement of the normal heart, or displacement of the trachea, aorta and oesophagus did not affect the contour of the diaphragm unless the pericardium was matted to the diaphragm. Extensive adhesions, with the heart often pulled over, generally to the side involved, makes the lung more favorable for thoracoplasty than an operation on the phrenic nerve. Not infrequently artificial pneumothorax is a futile procedure.

Lesions of the lower lobes more readily cause a disparity of the costal flare than the same amount of infiltration in the upper lobe. Adhesive pleurisy is a factor to consider in either case. Normal chests often show a slight disparity in the outward movement of the two costal margins, but there is present a freedom of motion that is not present when there is active or quiescent disease. Infiltration, which is truncal, scattered and isolated, or moderate hilar disease may not cause discernible impairment of the extensibility of the lung. In such cases, other findings being ques-

tionable, the stereoscopic X-ray proves to be the only satisfactory evidence for a conclusive diagnosis. Ninety-four per cent of the cases in this series demonstrated disparity in the costal-margin movement. Eighty-four per cent showed the costal margin on the side most involved to move at a lesser distance from the median line.

In spite of our modern methods, equipment and early-diagnosis campaigns, the diagnosis of pulmonary tuberculosis is too often deferred in both definite and border-line cases. Hoover's costal margin phenomenon, because of its constant presence, can be utilized at the bed-side of every patient, with advantage to all concerned.

CONCLUSIONS

1. Since the diaphragm is the most important muscle of respiration, it should receive consideration in the diagnosis of tuberculosis and its complications, and in selecting any subsequent surgical procedure.

2. In infiltrating conditions of the lung, particularly tuberculosis as herein stated, there is disparity in the outward movement of the costal margin.

3. In the greater percentage of cases diminished movement will be on the side of the most involved lung, when compared with the movement on the opposite side.

4. The disparity of movement is due, not only to the abnormal alterations in the arch of the diaphragm, and greater or lesser activation of the diaphragm, but also to the deactivation of the intercostal muscles.

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THE COMPLEMENT-FIXATION TEST IN DIFFERENT CLINICAL MANIFESTATIONS OF TUBERCULOSIS[1]

TH. THJÖTTA AND EDV. GUNDERSEN

Since the discovery in 1903 by Bordet and Gengou (1) that sera from tuberculous individuals contained antibodies reacting specifically with the tubercle bacillus, an intense investigation has been carried on in the hope of finding a complement-fixation test for tuberculosis similar to that later worked out for syphilis. It was soon demonstrated, however, that the test for tuberculosis was not specific to the extent of the Wassermann test in syphilis. Subsequent studies brought out the fact that sera from tuberculous individuals often gave positive complement-fixation tests with other acid-fast bacteria, such as the lepra, smegma and timothy bacilli, as well as with the diphtheria bacillus. Again very often sera from patients with obvious tuberculous lesions gave negative complement-fixation tests with antigens prepared from tubercle bacilli.

A variety of antigens have been employed, including living and dead tubercle bacilli, saline and alcoholic extractions of the bacterial cells, and culture fluid as well as the whole culture. Different manipulations have been tried to destroy the capsule surrounding the bacterial body, such as washing the bacilli in ether, acetone or tetraline, or by extractions in the Soxhlet apparatus according to the technique of Dreyer (2). Finally Wadsworth (3) and his coworkers attempted to isolate the specifically reacting bodies of the bacterial cell by laborious chemical processes. These studies seemed very promising and indicated that the acetone-insoluble lipoids of the tubercle bacillus contain the antigenic property of the bacterial body. The antigens of Wadsworth seem to give very good fixations in sera from tuberculous individuals and animals suffering from artificial tuberculous infection. The nonspecific reactions with these antigens seem to be negligible.

EXPERIMENTAL METHODS, MATERIALS AND RESULTS

The antigens used in these studies were prepared by drying the bacterial cells obtained from glycerol-broth cultures, washing the dried cells

[1] From the Bacteriological Laboratory of the Norwegian Army, Oslo, Norway.

in ether, or by extracting with acetone in a Soxhlet apparatus according to Dreyer's method (2). Another lot of antigens has been prepared according to Wassermann's technique, by adding ovolecithin to the ether-treated bacterial cells (4). Antigens prepared by these various methods have been alternately tried in our investigations. We have not been able, however, to detect any principal difference in their complement-fixing ability.

Human and bovine tubercle bacilli have been employed in these studies and both these antigens have given the same percentage of positive tests.

The dried bacterial cells prepared in accordance with the above-mentioned methods are then suspended in normal saline solution in a concentration by weight of 1:100. As a rule the anticomplementary titre of this emulsion is 0.012 cc. when every other factor of the test is 0.1 cc. In this manner the entire amount of fluid in the test is 0.5 cc. when the suspension of sheep corpuscles and haemolytic serum are included. One-fourth of the anticomplementary titre is used in the final complement-fixation test. A determination of the anticomplementary titre is made before every single test, and by this procedure the amount of antigen varies according to the result of each preliminary test.

A long series of tests has been carried out with sera obtained from healthy individuals and from syphilitics with a strongly positive Wassermann test. For these control tests we have used sera from patients definitely known to be nontuberculous. Every new lot of antigen has been examined in this manner, and we have not found any nonspecific complement fixation with these sera.

We are, however, willing to admit the possibilities that in a series of several hundred tests with sera obtained from syphilitics one might encounter some nonspecific tuberculous fixations. In such cases one must consider the possibility of coincidental tuberculous and syphilitic infection. To avoid this complication we have used only sera from our own patients who showed no tuberculous manifestations.

The specific titre of sera from pulmonary tuberculosis was regularly 1:50. This titre is not very high, but it is distinctly reliable. Such is not always the case with antigens rich in lipoidal constituents, like that of Besredka (5). As is well known, this antigen consists of the whole culture on Besredka's tubercle-bacillus medium, which is a distilled-water emulsion of the alkalinized yolks of eggs. In our tests this antigen has given positive fixations in a titre of 1:400 with sera from pulmonary tu-

berculosis. But this antigen has also given high nonspecific titres with sera from syphilitics. In one of our tests we found that it gave a higher positive complement-fixation with a syphilitic serum than with serum from a case of lupus vulgaris. Although this fact has been stressed by different workers, the Besredka antigen has nevertheless gained wide popularity. This seems unjustifiable, if it is correct that the antigen may give 33 per cent of nonspecific tests with sera from syphilitics, according to Silberstein (6), and 4 per cent of nonspecific tests in normal sera, according to Venturi (7).

Although in our own control tests our antigens do not show as high a titre as that obtained with the Besredka antigen, we are better satisfied with the antigen of acetone-extracted, dried bacterial cells than with the Besredka antigen. We will, therefore, not report any of the results obtained with the Besredka antigen. We feel confident that the results obtained with our special antigens are quite specific, since positive tests in pulmonary tuberculosis cover a very large part of the specimens.

Our purpose has not been to make a sole investigation of the diagnostic value of the complement-fixation test in the different clinical manifestations of tuberculosis, but also to try to gain some information about the immunizing forces at work in the different clinical manifestations of tuberculosis as determined by the test. It was especially desirable to see whether or not tuberculous manifestations of the skin would show any degree of positive tests and again to determine whether these manifestations might yield a lower percentage of positive tests than would manifestations of the internal organs. To obtain the necessary controls, we made the same tests with sera from patients suffering with all types of tuberculosis. The interest in these results centres in the ratio found to exist between the positive tests in different clinical manifestations of tuberculosis. This proportion must be considered very reliable, since the tests from the different sources have been made simultaneously by the same investigators employing an identical technique.

Our material consisted of 325 specimens of blood-serum obtained as follows: (1) 101 sera from pulmonary tuberculosis, (2) 106 from surgical tuberculosis, and (3) 118 from tuberculosis of the skin.

1: Pulmonary Tuberculosis

The tests under this heading fall into two parts. One consisted of 70 specimens obtained through the courtesy of Professor P. Bull from the Surgical Division B, Rikshospitalet in Oslo. These specimens were

from patients on whom thoracoplastic operations had been performed. This material is quite homogeneous, since each case is controlled in every possible detail and no false clinical diagnosis is included. The other part of the tests on cases of pulmonary tuberculosis consisted of 31 cases gathered from hospitals in Oslo and its vicinity. The material in the second part may possibly contain cases of chronic nontuberculous pulmonary disease, which were definitely excluded from the cases included in the first part.

The positive tests in the first part were 94.6 and in the second part 83.6 per cent. The first figure, which we shall regard as the more correct, is very high and approximates very closely the percentage found by Wadsworth in selected cases of pulmonary tuberculosis, namely 95 per cent. Our 94.6 per cent must then be considered the standard of positive results in our investigation, and the results seem to assure the reliability of our tests and the technique employed.

A peculiar phenomenon observed in relation to the tests on sera from patients, on whom thoracoplastic operations have been made, must be mentioned here. It is well known that thoracoplasty in tuberculosis is not infrequently followed by high temperature and severe toxic symptoms, during which the patients often succumb. Generally the onset of these symptoms is very sudden, and occurs during the first twenty-four hours after the operation without any intercurrent infection being actually found as the cause. In explanation of this phenomenon Bull and Thjötta (7) have advanced the theory that the cause is an intoxication due to the absorption into the circulation of tuberculous toxins from the collapsed lungs, a condition that would correspond to the constitutional reaction following large doses of tuberculin. It was thought that the phenomenon would be rendered less likely if the operation was performed in two stages, so that compression of the lung might take place less abruptly. This reasoning was found to be correct, and the reaction following thoracoplasty has been much milder by means of this technique.

Complement-fixation tests were performed before and after every operation in order to find out whether this theory could be strengthened by some laboratory method. The argument favoring this view was that antigens capable of uniting with antibodies within the human body might be driven over into the circulation after the compression of the lung. It might then perhaps be shown that the complement-fixation test would give a somewhat lower titre after the operation than before it. A decrease in the complement-fixation titre was actually observed in 80 per

cent of the tests. Seventeen per cent showed the same titre both before and after operation, while 3 per cent showed a higher titre after than before operation. It must be mentioned, however, that the cases on which these tests were performed were operated on in two stages, since the clinician considered this the best possible method. Accordingly the toxic symptoms were not so fully developed in these cases as they might have been if the operation had been performed in one stage. It is consequently believed that the serological differences before and after operation were more or less obscured by following this technique.

Table 1 illustrates a selected case before and after the two stages of operation. In this case the complement-fixation titre sinks from 1:50 to 1:25 and after the last stage the test is negative.

TABLE 1

Complement-fixing property and opacity in serum of a case of pulmonary tuberculosis before and after the two stages of thoracoplastic operation

DILUTION OF SERUM	FIRST STAGE						SECOND STAGE					
	Before			After			Before			After		
	1:10	1:25	1:50	1:10	1:25	1:50	1:10	1:25	1:50	1:10	1:25	1:50
Complement fixation....	+	+	+	+	+	−	+	+	−	−	−	−
Opacity of serum.....	+++			++			+			− Clear		

Another phenomenon observed in these tests is described here because we have not seen it mentioned in the literature. It consists of a regular change in opacity of the serum after operation. Before the first operation the sera are regularly quite opaque, but after the first stage this opacity changes from +++ to ++. Before the second stage the opacity is further decreased to +, and after this stage it disappears as a rule, and the serum becomes clear. Thus the curve of density of the serum takes a course similar to that observed in complement-fixation reactions. Therefore, the problem which must be explained is whether or not these two phenomena are both the result of mechanical changes following the operation, or whether, on the other hand, they may both be caused by the alcohol-ether narcosis used during the operations. This possibility may not seem altogether absurd, inasmuch as it is well known that a positive-Wassermann serum may change to negative after a large ingestion of alcohol. However, this notion will seem less probable in

regard to the opacity when it is remembered that the clearing up of the serum persists between the two stages of the operation. The phenomenon of opacity will be made the subject of further study.

2: Surgical Tuberculosis

Our material from surgical tuberculosis consisted of 106 specimens of blood obtained from the Kysthospital for Tuberculosis at Fredriksvern. We are indebted to Dr. Halfdan Sundt, physician-in-chief, for cordially placing his large clinical material at our disposal. The specimens in this group originated from patients suffering from spondylitis, tuberculosis of joints, bones and lymph nodes, and osteomyelitis of presumed tuberculous origin. It is possible, however, that these cases, with the exception of those of spondylitis, may have included some of nontuberculous aetiology. We have therefore arranged them into two groups, the one embracing 63 cases of spondylitis and the other 43 miscellaneous cases. The complement-fixation test was positive in 44 per cent in the first group and 27.5 per cent in the second group.

It should be mentioned that 51 cases (82.5 per cent) of spondylitis showed other tuberculous manifestations besides spondylitis or had shown such signs earlier. The clinical and roentgenographic examinations of these cases fully confirmed the clinical diagnosis. All gave negative Wassermann tests. It is therefore evident that, according to our technique, definite cases of tuberculous spondylitis did not yield more than 44 per cent of positive tests.

The other group of surgical tuberculosis gave only 27.5 per cent of positive tests or half of the positive results of the first group. The reason for this difference may be that not all of these cases were tuberculous. On the other hand, one may also consider the possibility of minor tuberculous involvement in this group, such as inflamed lymph nodes, and smaller foci in bones and elsewhere in the body.

3: Skin Tuberculosis

Under this heading 118 cases have been examined and arranged in the following groups: (1) 73 cases of lupus vulgaris, (2) 20 cases of lupus erythematodes and (3) 24 cases of miscellaneous tuberculosis including papulonecrotic tuberculides, erythema induratum, scrofuloderma, tuberculous ulcers, etc.

A: Lupus Vulgaris: All the cases under this heading and all other

cases of tuberculosis of the skin are gathered from the Dermatological Division of Rikshospitalet in Oslo through the generous coöperation of Professor E. Bruusgaard. The material is most valuable on account of the painstaking thoroughness with which all cases were examined in regard to clinical and roentgenographic details, especially of the lungs and peribronchial lymph nodes. These examinations very often showed old calcified foci of these organs as the result of tuberculous infection in early childhood. If a manifest lesion of the lung is found, the clinical course of this is a slow, mild and afebrile condition with sclerotic, avirulent development.

In 50 out of 73 cases of lupus vulgaris such old lesions were found in the lungs and peribronchial lymph nodes. Nine of the 73 cases gave a positive complement-fixation test, and all these except one showed old tuberculous lesions of the lungs. Moreover, one case had spondylitis and gave a titre of 1:50. The other complement-fixation tests were only slightly positive at 1:10 dilution.

The positive tests in ascertained cases of lupus vulgaris are therefore 12.3 per cent, a figure that corresponds well with that of Förtig (9), who found 10.7 per cent in the same group.

It is obvious that the concentration of complement-fixing antibodies in the blood of patients suffering from lupus vulgaris must be very slight as compared with the same feature in patients with pulmonary and surgical tuberculosis. Only occasionally is a positive test met with, and then as a rule in patients who show signs of other types of tuberculosis. Only at times may one expect to find a case with healthy lungs and positive complement-fixation test. These cases are generally negative. One of our cases, for instance, showed a lupus lesion covering large areas of the lower extremities. However, the lungs were not involved, and the complement-fixation test was completely negative.

B: Lupus Erythematodes: Twenty cases of lupus erythematodes have come to examination and 4 showed positive complement-fixation tests. Three of the cases with positive tests had also pulmonary tuberculosis, while one case did not show any lesions of the lungs, but suffered from a widespread acute skin infection. All the other cases had normal lungs and presented negative tests.

C: Miscellaneous Tuberculosis of the Skin: Among 24 cases of miscellaneous tuberculosis of the skin only one showed a positive test, namely, a case suffering with generalized, acute, papulonecrotic tuberculides.

DISCUSSION

Figure 1 illustrates our material. The dark columns represent the three main groups of pulmonary, surgical and skin tuberculosis. The white columns show the groups that are less reliable in regard to diagno-

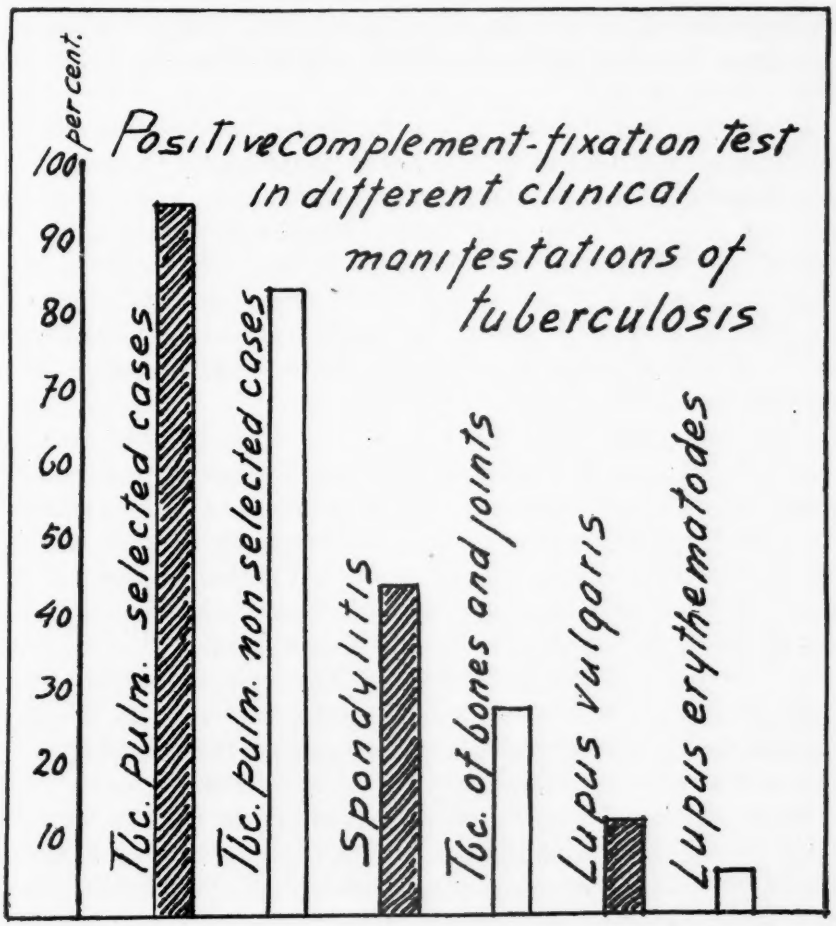

FIG. 1

sis and therefore less dependable as to results. In our three main groups every case has been thoroughly controlled and is a true case of the disease it represents. The cases of skin tuberculosis mentioned under paragraphs *3 B* and *C* are also definite cases, but are discussed separately, since only a few cases in each diagnostic group have been examined.

It will be seen that each of the three main groups consists of approximately the same number of cases, namely 70, 63 and 73 in the respective groups. As was mentioned earlier in this paper, all these cases were examined according to the same technique and by the same investigators. Every precaution was thus taken to ensure reliable results in regard to the proportion of positive tests within the 3 groups. The percentage was as follows: Pulmonary tuberculosis 94.6, surgical tuberculosis 44.0, and skin tuberculosis 12.3.

It is obvious from these figures that the diagnostic value of the complement-fixation test must be very limited in its application to tuberculosis as a disease. Only in pulmonary tuberculosis may one expect about 90 per cent of positive tests. In a disease like pulmonary tuberculosis the clinical, roentgenographic and microscopic findings will enable the clinician in almost every case to make a true diagnosis. It is unlikely, therefore, that a laborious serological test which fails in about 10 per cent should be very much needed. As a rule the test will only confirm what the clinician already knows.

Still more unsatisfactory was the result in surgical tuberculosis, in which only 44 per cent of true tuberculous spondylitis gave positive tests. And under this very heading we find many obscure clinical manifestations which are diagnosed as most likely tuberculous in origin, but are difficult in regard to their exact diagnosis. It is then evident that the clinician can rely very little on a test in which every other definite case of the disease (and even worse) will yield a negative result.

In tuberculosis of the skin the diagnosis is as a rule readily made by an experienced clinician, and no serological test is needed. But, if it were needed, the 12.3 per cent of positive tests among definite tuberculosis cases would certainly prohibit its use as a diagnostic aid.

In the absence of a better technique than the one followed by us, it must be said that the complement-fixation test in tuberculosis is only of moderate value in pulmonary tuberculosis. In all other manifestations of tuberculosis it is of no diagnostic value.

It must, however, be anticipated that the new technique of Wadsworth may alter this condition, but one might well question whether such realization is possible. It is obvious that Wadsworth, with his elaborate technique, does not record more positive tests in pulmonary tuberculosis than we are able to do with our technique. It must therefore be admitted that in pulmonary tuberculosis our percentage lies as high as may reasonably be expected. And when the other manifestations of tuberculosis

give only a very few positive tests, and then almost always in patients that suffer from pulmonary tuberculosis beside their other manifestations, it seems justifiable to believe that the body does not produce complement-fixing antibodies in miscellaneous tuberculous manifestations other than pulmonary tuberculosis to so great an extent that a positive test can be obtained. It must be said further that a positive test in these other manifestations depends upon the presence or preëxistence of pulmonary tuberculosis.

Even if the technique is so much further developed that the missing 10 per cent might be recovered in complement-fixation tests on pulmonary tuberculosis, it is still very far from the 44.0 or 12.3 per cent, respectively, up to 100 per cent in the other tuberculous manifestations.

When it has been anticipated that the complement-fixation test in tuberculosis might be developed to the extent that it should bring the clinician the same help in the diagnosis of this disease as the Wassermann test has done in syphilis, it is at once obvious that too close a comparison has been made between these two tests. This is not justifiable, however, since the antigens are principally different. It would be more appropriate to compare the complement-fixation test in tuberculosis with the same tests in gonorrhoeal complications or in glanders, in which the diagnostic value is less than in the Wassermann test in syphilis.

When tuberculous manifestations in organs other than the lungs, such as in the joints, bones, skin and the like, do not produce any degree of complement-fixing antibodies, the reason may be sought in the slow clinical course of these manifestations. These cases are as a rule afebrile and atoxic. It might also be argued that the lungs on account of their large volume and richness in blood supply are more antibody-productive than the bones, joints and skin.

The complement-fixation text in tuberculosis does not seem to be of any real value as an index of immunizing forces in the different manifestations of the disease. It is obvious that a case with old healed lesions in the lungs and a persistent spondylitis or lupus, but with a negative complement-fixation test, must show a higher immunity against the disease than a case of progressive pulmonary tuberculosis with a positive complement-fixation test. The last case should rather be compared with a patient suffering from an acute bacterial disease, for instance, typhoid fever, with a positive Widal test and complement-fixation test, while the patient with spondylitis or lupus should be compared with a

patient having recovered from a typhoidal infection some time previously and showing a negative test, but still harboring a typhoidal abscess or being a typhoid carrier.

CONCLUSIONS

1. Three hundred and twenty-five sera from cases with different manifestations of tuberculosis have been examined for their complement-fixing ability. These tests fall under three main headings, namely, pulmonary, surgical and skin tuberculosis. The percentages of positive tests in the three groups are 94.6, 44.0, and 12.3, respectively.

2. Only cases with pulmonary tuberculosis show a relatively high percentage of positive tests. In the other manifestations the positive tests seem to depend mostly upon the presence or preëxistence of tuberculosis of the lungs.

3. The complement-fixation test in tuberculosis cannot be compared with the Wassermann test in syphilis, but rather with the same test in other bacterial infections when the specific microbe is used as an antigen.

4. The antigens used in these studies, namely, dried acetone-extracted bacterial cells suspended in normal saline solution, have given the same proportion of positive tests as those obtained with the more elaborate antigens of Wadsworth, which consist of acetone-insoluble lipoids of the tubercle bacillus.

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OBSERVATIONS ON THE OCCURRENCE OF NON-SPECIFIC AGGLUTININS IN TUBERCULOSIS[1]

ROBERT A. KILDUFFE AND WILLIAM W. HERSOHN

While it has long been known that the production of major agglutinins following the introduction of *B. typhosus* into the body is an expression of an immune phenomenon possessing a high degree of specificity, it is also known that the clinical application of this phenomenon in the study of typhoid fever and related infections is subject to a number of exceptions.

These exceptions are, in the main, dependent upon the fact that when a specific antigen, such as, for example, *B. typhosus*, is introduced into the body, there are produced, in response, two sets of antibodies: (1) the major antibodies, in this case, agglutinins, and (2) the minor antibodies or, in this case, "group" agglutinins.

As a result of this production of group or heterologous antibodies not only *B. typhosus* but also the other more or less similar bacilli may be agglutinated and, what is of somewhat more immediate clinical application, this process may be reversed, so that, because of the presence of heterologous agglutinins, *B. typhosus* and its congeners may be agglutinated by the serum of individuals not suffering from typhoid infection but from certain other diseases.

The explanation of this heterologous agglutination depends upon two factors: (1) the Ehrlich theory of the construction of agglutinogens and agglutinins; and (2) the theory advanced by Durham (1) concerning the complexity of the structure of receptors.

According to Ehrlich's theory an agglutinogen contains receptors of the haptophore group and an agglutinin contains receptors of the zymophore group, and, according to Durham, a receptor is a complex body which may be split into various component parts, each of which may exhibit an individual structure and have independent action.

In accordance with these conceptions, if the bacillary constituents or receptors are designated as *a*, *b*, *c*, *d* and *e*, and the serum constituents (agglutinins, receptors) are designated as *A*, *B*, *C*, *D* and *E*, it is obvious

[1] From the Laboratories of the Atlantic City Hospital, Atlantic City, New Jersey.

that if a serum containing receptors *A*, *B*, *C*, *D* and *E* of the zymophore (agglutinin) group is added to a bacillary culture containing receptors *a*, *b*, *c*, *d* and *e*, of the haptophore (agglutinogen) type, the resultant agglutination will be maximum because all of the receptors correspond and combine.

If, on the other hand, the serum is added to a bacillary culture containing only *c*, *d* and *e* receptors, while agglutination may occur, it will not be complete but partial, as only the receptors *C*, *D* and *E* are available for combination. As Durham has pointed out, this partial or heterologous agglutination may be still further complicated by the number of different receptors in different strains of the same microörganism as, for example, in one strain there may be receptors *10a*, *5b*, *2c*, *1d* and *1a*, whereas in another strain they may be *1a*, *2b*, *3c*, *4d* and *10e*.

That group agglutinins and group agglutination exist is a matter of fact, and that group and nonspecific agglutination may occur in the Widal test in the absence of typhoid infection is a fact common to the knowledge of any serologist.

Regardless of the nature or satisfactory character of the explanations advanced for its occurrence, among the diseases in which nonspecific Widal reactions have been noted in greater or less degree is tuberculosis.

In a recent communication upon the subject Yamaguchi (2) reported that the blood-serum of pulmonary tuberculosis in all its stages agglutinated typhoid bacilli, often in high dilutions, and that there was some apparent relation between the severity of the symptoms and the titre of the agglutination.

As, according to a somewhat uncertain impression, this had not been the previous experience of the senior author (R. A. K.), the following study was undertaken and is herewith reported.

The specimens of blood from cases of pulmonary tuberculosis were obtained from two sources: the Atlantic County Tuberculosis Hospital, Medical Director, C. M. Fish, M.D., and the State Tuberculosis Sanatorium, Hopemont, West Virginia, J. G. Pettit, M.D., Medical Director.

To these and to Mr. L. E. Neal, technician in the laboratories of the latter institution, who collected and forwarded the sera, our thanks are due and hereby acknowledged.

In all, a total of 200 sera from tuberculosis patients were examined in accordance with the following plan:

1: In order to ascertain the correlation, if any, between the presence and degree of agglutination, all cases were classified as (a) incipient, (b) moderate

and (d) far advanced, and the temperature and clinical condition of the patient noted at the time the specimen was collected.

2: For the same reason inquiry was made as to the presence or absence of any intercurrent infection.

3: Inquiry was also made as to the administration of typhoid vaccine, or the occurrence of typhoid fever in the patient's past medical history.

All sera were tested for agglutinins for *B. typhosus*, *B. paratyphosus A*, *B. paratyphosus B*, *B. proteus X-19*, and *B. abortus* (Bang), and, incidentally, subjected to the Kahn and Wassermann (Kolmer *quantitative technique*) tests. When typhoid or paratyphoid agglutination was encountered the faeces were cultured for these microörganisms or other pathogens.

The results of the investigation follows:

Number of sera containing agglutinins	89 or 44.5 per cent
Number of sera agglutinating *B. typhosus*	58 or 29.0 per cent
Number of sera agglutinating *B. paratyphosus A*	5 or 2.5 per cent
Number of sera agglutinating *B. paratyphosus B*	24 or 12.0 per cent
Number of sera agglutinating *B. proteus X-19*	2 or 1.0 per cent
Number of sera agglutinating *B. abortus* (Bang)	0 or 0.0 per cent

The agglutination tests in all instances were macroscopic and quantitative, the serum being tested in dilutions of from 1:10 to 1:160.

The titres of the positive reactions were as follows:

Microörganism	*Maximum*	*Minimum*	*Average*
B. typhosus	1:160	1:20	1:73.7
B. paratyphosus A	1:80	1:20	1:40
B. paratyphosus B	1:80	1:20	1:54.1
B. proteus X-19	1:80	1:40	1:60

In the sera agglutinating the microörganisms of the typhoid group the distribution of agglutinins was as follows:

Sera agglutinating *B. typhosus* alone	45 or 22.5 per cent
Sera agglutinating *B. typhosus* and *B. paratyphosus A*	3 or 1.5 per cent
Sera agglutinating *B. typhosus* and *B. paratyphosus B*	7 or 3.5 per cent
Sera agglutinating *B. typhosus* and *B. paratyphosus A* and *B*	1 or 0.5 per cent
Sera agglutinating *B. paratyphosus A* and *B*	1 or 0.5 per cent

It is of practical interest to determine in the case of the agglutinins for the typhoid group whether these were entirely heterologous or specific,

and, if so, to what degree. To this end an effort was made to ascertain whether any of these patients had had typhoid fever or typhoid vaccine. The results of this inquiry are shown below.

Of the 45 patients whose sera agglutinated *B. typhosus* only 15, or 33 per cent, had had typhoid fever and 12, or 26 per cent, had had typhoid vaccine at some time in their previous history. In 21, or 46 per cent, no history of either could be obtained, and efforts to isolate microörganisms of the typhoid group from the stools (one specimen) were unsuccessful.

Of the three sera agglutinating *B. typhosus* and *B. paratyphosus A* one had had typhoid vaccine and in two no history of typhoid fever or vaccine was obtainable. Culture was unsuccessful in the latter two cases.

Of the seven sera containing agglutinins for *B. typhosus* and *B. paratyphosus B*, one had had vaccine and the history and culture in the others were negative.

One serum agglutinating all three microörganisms of the typhoid group was from a patient who had had typhoid fever.

Of 5 sera agglutinating only *B. paratyphosus A*, one was from a patient who had had typhoid vaccine, and another from a patient who had had typhoid fever. A similar history was obtained from three patients whose sera agglutinated only *B. paratyphosus B*, while the patient whose serum agglutinated *B. paratyphosus A* and *B* had no history of either vaccine or typhoid infection.

A positive faeces culture was not obtained in any instance.

In view of Yamaguchi's conclusion of a correlation between the presence of heterologous agglutinins it is of interest to note the classification, temperature, and presence of intercurrent infections in the patients whose serum contained agglutinins, presumably heterologous, and in whom the history and culture were without significance with reference to typhoid infections, and the two cases whose serum agglutinated *B. proteus X-19*.

In one case the diagnosis of tuberculosis was questionable and remained to be proved, two were classified as "fibroid, arrested," two were incipient, nine were far advanced, and by far the greater number were in the group of moderately advanced cases.

In the majority of cases the temperature at the time the specimen was taken approximated normal (97° to 99.5°F.), the highest temperature recorded in any agglutinin-positive case being 100°F. On the other hand, none of the cases in which the temperature was over 101° showed the presence of any agglutinins.

Intercurrent infections were absent in all but one case (pneumonia), agglutinins being absent in this one.

RESULTS

1. Nonspecific, heterologous agglutinins may be produced in tuberculosis for microörganisms of the typhoid group and, infrequently, for *B. proteus X-19.*

2. There was no apparent relation between the presence or amount of agglutinins and the character or clinical course of the tuberculous infection.

3. The occurrence of agglutinins for microörganisms of the typhoid group is not *per se* conclusive evidence that they are nonspecific, or heterologous in origin, as, in a definite number of such cases, the patient will be found to have had typhoid fever or to have received antityphoid vaccine.

4. Heterologous agglutinin-production in pulmonary tuberculosis is of relatively infrequent occurrence and without apparent relation to the clinical course of the disease.

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A NOTE ON THE OCCURRENCE OF POSITIVE WASSERMANN AND PRECIPITATION REACTIONS IN PULMONARY TUBERCULOSIS[1]

ROBERT A. KILDUFFE AND WILLIAM W. HERSOHN

In the application of any laboratory procedure to the diagnosis or study of disease it is always of interest and importance to know the effect of intercurrent infections upon the relative specificity of the procedure.

This is of particular interest in the serological procedures utilized in the study of syphilis and, while the effect of tuberculosis upon the Wassermann and precipitation tests for syphilis have been commented upon by numerous observers, the following note is recorded as of some interest.

During the course of a study of the incidence of nonspecific agglutinins in pulmonary tuberculosis (1) both precipitation and complement-fixation tests for syphilis were applied to the sera with results noted below.

In all 200 sera were examined from patients in all stages of pulmonary tuberculosis. The specimens were obtained from the Atlantic County Tuberculosis Hospital, Northfield, New Jersey, through the coöperation of C. M. Fish, M.D., Medical Director, and the State Tuberculosis Sanatorium, Hopemont, West Virginia, through the coöperation of J. G. Pettit, M.D., Medical Director, and the laboratory technician of the latter institution, Mr. L. E. Neal.

The complement-fixation test was the quantitative procedure described by Kolmer (2), which is the routine method in these laboratories. The precipitation test was the microtest described by Kline and Young (3) which previous experience had shown to be useful and reliable (4).

Only one anticomplementary reaction was encountered, and of this serum there was insufficient quantity to permit the use of the precipitation test.

[1] From the Laboratories of the Atlantic City Hospital, Atlantic City, New Jersey.

Negative reactions to both tests were obtained with 191 sera and positive reactions were obtained with 8 sera as shown below:

Kolmer	*Positive reactions Microprecipitation*
40000	+
00000	++
44400	++
00000	±
44420	+++
44400	++++
44100	++
44400	++++

It will be noted that there were two sera negative to the complement-fixation test but reacting to the precipitation test. The plus-minus precipitation reaction is regarded by all competent observers as without diagnostic significance, and in this case there was neither clinical nor historical evidence of syphilis. The other serum in which a plus-two precipitation reaction was obtained illustrates anew the fact common to the knowledge of all serologists: that, on a single test, a syphilitic serum may be positive to one reaction and negative to the other, and *vice versa* upon subsequent occasions; or, in other words, either procedure may give a false negative reaction in a small percentage of cases.

In all the remaining cases reacting positively corroboratory evidence as to the specificity of the reaction was obtainable and false or non-specific reactions did not occur.

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Pearl Mitchell Hall

1860-1928

Pearl Mitchell Hall was born in West Jefferson, Ohio, October 19, 1860. When he was thirteen years old his father, Reverend Levi Hall, and his mother, Lucinda Hall, moved to Austin, Minnesota, where the family resided for two years before moving to Minneapolis. The son attended the University of Minnesota but later transferred to the Hahnemann Medical College in Chicago. From this institution he received his M.D. in 1882. After graduation, Doctor Hall returned to Minneapolis to enter medical practice, and was the same year married to Anna C. Depew.

In 1884 he became attending physician at Sheltering Arms, where he served for thirty-four years. He was in 1885 appointed to the Minneapolis City Hospital staff, a post that he held for thirty-three years. To both of these positions he donated his time and energy without financial remuneration in order to be helpful to the community. Because he served the people so willingly and so faithfully, attention was attracted to him as evidenced by his appointment to the Minnesota State Board of Medical Examiners only five years after his graduation. In 1898 he was made medical inspector in the Minneapolis Health Department, and held this position only three years, when he was promoted to be commissioner of Health of the City of Minneapolis.

At this time garbage disposal was a tremendous problem. Doctor Hall was of the opinion that the best solution would be to have all garbage wrapped in paper in the homes and the small wrapped packages placed in garbage cans, thus making it possible to burn all garbage. Much to the surprise of those who opposed him, the citizens gladly accepted his method of wrapping garbage. This neat and sanitary method of disposal under city collection has since been copied almost universally throughout the United States. Another worth-while accomplishment while Commissioner of Health was his establishment of public baths in the lakes of Minneapolis. After retiring from the office of Commissioner of Health and returning to private practice, Doctor Hall became the

Pearl Mitchell Hall

editor of *Health and Happiness*, a health-column of the *Minneapolis Tribune*.

It was while serving as Commissioner of Health of the city of Minneapolis that Doctor Hall's interest in tuberculosis was greatly increased. In 1908 he and Mrs. Christian worked out a nursing follow-up service, which was placed under the jurisdiction of the Health Commissioner and financed by Mrs. Christian. In January, 1912, the Board of Tax Levy appropriated sufficient funds to take over this work by the City Health Department. This service became so popular that now, under the direction of Doctor F. E. Harrington, Commissioner of Health, fifteen nurses are engaged in the work.

On May 1, 1909, Doctor Hall and Miss Elizabeth Sprague, R. N., opened the first special tuberculosis clinic in Minneapolis. This free service for needy patients was established at the Minneapolis City Hospital, where Doctor Hall remained an examiner and adviser for about three years. Time has so proved the need of such work that four well-equipped chest clinics are now in operation in Minneapolis.

Doctor Hall's interest in tuberculosis attracted so much attention that he was appointed a member of the Minnesota State Tuberculosis Advisory Commission, where he served faithfully until the Commission was abolished and its work taken over by the State Board of Control. In 1918 he was made Superintendent of the State Sanatorium near Walker, Minnesota.

Doctor Hall was a man who made friends everywhere. To the patients he was always friendly and sympathetic; it pained him terribly to refuse a patient a privilege. He was an optimist, and it was his nature to want to see others happy. He was a firm believer in education. In order to keep abreast of the times he sent a number of his assisting physicians to the Trudeau School for Tuberculosis at Saranac Lake; in fact he attended this school himself in the summer of 1920.

His institution was often spoken of as the Walker Sanatorium but it was located some distance from the town. A postoffice had already been established at the institution under the name of State Sanatorium, but Doctor Hall changed the name to *Ah-gwah-ching*, from an Indian name meaning "out-of-doors." Since the name was rather difficult to spell and pronounce, it was some time before the people of the state became familiar with it. He was not only interested in the activities of the institution but in those of the entire community. He did much to promote the public welfare of Walker and had many close friends in that town.

He was a member of many professional organizations, among them the Upper Mississippi Valley Medical Association, the Minnesota State Medical Association, the American Medical Association, the American Public Health Association of which he was one time chairman of the Municipal Health Officer section, the National Tuberculosis Association, the American Sanatorium Association, the Mississippi Valley Conference on Tuberculosis of which he was one time president, and the Minnesota Trudeau Medical Society of which he was president at the time of his death.

J. A. M.

THE CAUTERIZATION OF ADHESIONS IN ARTIFICIAL PNEUMOTHORAX BY THE JACOBAEUS-UNVERRICHT METHOD OF CLOSED PNEUMOLYSIS[1]

Observations on 100 Cases

RALPH C. MATSON[2]

A careful analysis of statistics furnishes most convincing evidence of the value of artificial pneumothorax in the treatment of pulmonary tuberculosis. However, its success is almost in direct proportion to the number and character of adhesions present, and preventing satisfactory collapse of the lung. According to our experience pleuritic adhesions cause more failures in pneumothorax therapy than any other complication, 40 per cent of its failures being caused by such adhesions interfering with satisfactory compression.

Adhesions, unfortunately, are most often distributed over the more diseased parts of the lung, being almost invariably present over superficial cavities. Thus, the very part of the lung which is in greatest need of rest or collapse is least likely to receive it. It is a frequent observation that a single string or band, extending from a partially collapsed lung to the thoracic wall, holds open a cavity and renders the attempted pneumothorax a failure. (Figures 1 and 2.)

The value of satisfactory pneumothorax in which adhesions did not prevent the closure of cavities or adequate rest of the lung as compared with partial pneumothorax in which adhesions did impede the mechanical and physiological benefits of a pneumothorax is shown in table 1.

Early in our experience we were convinced of the advisability of converting a partial pneumothorax into a satisfactory one, and for years we resorted to stretching the offending adhesions by gently increasing the intrathoracic pressure, since we regarded the open operations or closed operations under X-ray control, for the purpose of cutting adhesions, as

[1] From the Department of Medicine, University of Oregon Medical School, Portland, Oregon, and the Portland Open Air Sanatorium, Milwaukie, Oregon. Aided by a grant from Mrs. Henry F. Chaney and Mrs. C. H. Davis, Jr.

[2] This paper is based upon material from the combined service of the author and his associates, Dr. Ray W. Matson and Dr. Marr Bisaillon, who have rendered valuable assistance.

much too dangerous, and the result as not justifying the risk involved. At the same time, efforts to secure a satisfactory pneumothorax by stretching adhesions left much to be desired. The results on the whole were unsatisfactory, as is indicated in the results in our partial-collapse cases shown in table 1.

In 1913 Jacobaeus of Stockholm devised an ingenious method of dividing adhesions by means of a galvanocautery, introduced at one point through the chest-wall and operated under the guidance of a thoracoscope inserted through the chest-wall at another point.

The original Jacobaeus thoracoscope had a limited and reduced field of vision, making the operation difficult. In 1922 Unverricht developed a thoracoscope equipped with a Zeiss system of lenses that gave a superb view. Meanwhile, Jacobaeus has much improved his instrument, which now also gives a good view. And while the Unverricht thoracoscope has the advantage over the Jacobaeus instrument in that it gives a larger field of vision, it is at the same time more bulky, and radiates more heat from the larger light globe, which may introduce a factor in the formation of exudate. An attractive feature of the Jacobaeus instruments is that the cannulae for the thoracoscope and cautery are of the same size, so that either the thoracoscope or the cautery may be placed through a cannula after the trocar has been withdrawn. This permits an interchange of instruments during burning, and makes it possible to view the adhesions or burn them from two points without the necessity of more than two punctures, a procedure that may be advantageous in some cases of multiple adhesions. At the same time, the circumstance that only a straight-shaft cautery can be passed through the Jacobaeus cannula is a great inconvenience. We have found the curved-shaft cautery more applicable because it facilitates the approach to adhesions in any location.

A desirable feature perhaps of the Jacobaeus instruments is that sufficient space exists between the cautery shaft and the cannula to allow smoke to escape, and thus render it unnecessary to interrupt the operation in order to ventilate the pneumothorax cavity and rid it of smoke during the burning operation. However, a distinct advantage of the Unverricht outfit is the flexible cannula through which one may pass either a straight or curved-shaft cautery.

Since the perfection of technique of burning adhesions under thoracoscopic control, according to the method of Jacobaeus and Unverricht, we have employed this operative procedure during the last three years on all suitable cases.

The general impression is that operations for the division of adhesions are seldom really indicated. This is contrary to our experience. In a careful re-study of 91 cases now dead in our partial-collapse series, shown in table 1, we found that, from a roentgenological standpoint, 36 or 40 per cent were suitable cases for burning earlier in their pneumothorax career, and that, had they been operated upon, instead of resorting to the stretching of adhesions and prolonged partial-pneumothorax treatment, probably 50 per cent would be alive and well to-day.

Of 268 cases subjected to artificial pneumothorax during the past three years, adhesions prevented satisfactory pneumothorax in 69, or 25.9 per cent. Of this latter number, 31, or 45 per cent, proved suitable for the Jacobaeus-Unverricht operation. The other operated cases reported

TABLE 1

Comparative value of artificial pneumothorax in cases in which adhesions did not prevent adequate functional rest and closure of cavities, and those in which adhesions did prevent sufficient collapse of the lung to close cavities or give the necessary functional rest
Observations on 850 cases: January 1, 1911, to August 1, 1925

CHARACTER OF PNEUMOTHORAX	CLINICALLY WELL	ARRESTED	DEAD
	per cent	*per cent*	*per cent*
Satisfactory collapse, adhesions not preventing closure of cavities or adequate rest of the lung	48	20	21
Partial collapse, adhesions preventing satisfactory closure of cavities or adequate rest of the lung	13	13	50

in this paper were referred cases and those that began their pneumothorax treatment before we resorted to this operation.

TECHNIQUE

The preoperative preparation consists in a determination of the bleeding and coagulation time of the blood and blood-grouping. A pneumothorax refill should be done a day or two before the operation, so as to provide as large as possible a pneumothorax in which to work. The chest is prepared the night before operation by shaving, and an alcohol pack is applied as for a thoracoplasty. One-half hour before operation the patient receives, hypodermatically, morphine sulphate, gr. $\frac{1}{6}$ to $\frac{1}{4}$, in 2 cc. of 50 per cent magnesium-sulphate solution.

The surgical technique calls for careful observance of scrupulous asep-

sis such as obtains in other major thoracic operations. The instruments (figure 3), including cables, should be sterilized by formaldehyde. We have found the Wappler formaldehyde sterilizer, using formalin tablets decomposed by heat, to be the most satisfactory. The instruments should be sterilized the day before and wiped free of formaldehyde before the operation. There should always be 1000 cc. of sterile normal salt solution and 250 cc. each of 2.5 per cent and 5 per cent oil of gomenol at hand to be used, as commented upon later.

The patient is placed on the table with the pneumothorax side up and the good side resting upon a hard pillow. After painting with iodine or picric acid and alcohol, the patient is draped as shown in figures 4 and 5 for a posterior approach, which will be the point of entrance of the thoracoscope in the majority of cases, as most adhesions will be found in the posterior upper quadrant of the pneumothorax.

The operation is preferably done in an absolutely dark room, which not only improves the operator's vision, but the light from the thoracoscope will then illuminate the pneumothorax field like a Japanese lantern. The shadows of the ribs, as well as attachments of large adhesion-folds, are clearly visible, unless the pleura is too thick. Thus, valuable information may be gathered regarding the site of the attachment of adhesions to the chest-wall, and this will then serve as a useful guide for entrance of the cautery.

All instruments should be thoroughly tested beforehand, and the electrical currents adjusted to give the proper amount of light in the thoracoscope and heat in the cautery. A Wappler wall-transformer has proved most satisfactory for regulating the light- and heat-currents.

The point of entrance of the thoracoscope will depend entirely upon study of the stereoscopic films. One should introduce the thoracoscope at a point where the best view of all surfaces of the adhesions will be obtained. Because of the thickness of the muscles in the interscapular region, it is advisable to avoid this area. One seldom need go higher posteriorly than the 6th or 7th intercostal space. If a higher approach is necessary for study of apical adhesions, one may preferably introduce the thoracoscope anteriorly in the 1st or 2nd intercostal space.

The site of puncture, previously determined by a study of the stereoscopic films, is infiltrated with 1 per cent novocaine-suprarenin solution. It is unnecessary to anaesthetize the intercostal spaces above and below the site of puncture, but care should be taken to infiltrate the endothoracic fascia and secure a good anaesthesia of the parietal pleura. The

presence of a pneumothorax beneath the site of puncture should be verified by passing the needle through the chest-wall and aspirating air with the syringe.

A one-centimetre incision is made with an iridectomy knife through the skin. This incision should be made in the direction of the external intercostal fibres, so that the puncture site may be closed with a single catgut suture, including the thoracic fascia and some of the fibres of the external intercostals, if possible. The trocar and ball-valve cannula for the thoracoscope is pushed gently through the chest-wall. (Figure 6.) Every precaution must be exercised to avoid plunging the trocar into adherent lung, adhesions or other structures. After withdrawing the trocar, the thoracoscope is introduced with the lens up so as not to smear it with the usual drop or two of blood which runs down the cannula from the chest-wall puncture. It is furthermore advisable to introduce the thoracoscope in as nearly a horizontal direction as possible.

Keeping in mind the stereoscopic image, one should study adhesions which are of technical importance with great care. (Figure 7). One must have complete orientation regarding their position and direction with relation to the chest-wall and collapsed lung, as well as their dimensions, configuration, and distance from the lens and other anatomical structures. It is particularly necessary to know how close the point of cauterization is to large blood-vessels and important nerve-trunks. The presence of lung tissue, blood-vessels and tuberculous deposits in the adhesions to be burned should be determined, following which a study should be made of the inner chest-wall and that site selected for entrance of the cautery which will give an unobstructed view and permit placing the cautery in the most advantageous position across the adhesion at a right angle for purposes of burning. (Figure 8). If multiple adhesions are present, particular care must be exercised that the cautery is introduced at a point most favorable for attacking all adhesions. One must especially avoid entering the cautery at a point where adhesions prevent its being seen, as, for instance, on the blind side of adhesions. (Figure 9).

The point of entrance of the cautery will depend entirely upon the thoracoscopic findings, but, as a rule, the cautery can be most advantageously introduced in the axillary line,—the more anteriorly, the better, as the intercostal spaces are wider toward the front and permit a greater degree of manipulation.

After selecting the site of entrance for the cautery, the area is infiltrated with novocaine-suprarenin. If the operator is properly orientated, he

may observe through the thoracoscope the needle of the infiltrating syringe emerging through the pleura. The needle should then be withdrawn until it disappears from the pleura into the endothoracic fascia, which should be thoroughly infiltrated with the anaesthetic. This infiltration will be seen through the thoracoscope as a blanched area elevated like a wheal on the inner chest-wall. Good anaesthesia of the parietal pleura and chest-wall is desirable, as heat from the cautery shaft is likely to be painful. The trocar and cannula for the cautery are then introduced. A cautery is selected, either curved or straight, which will give the best approach to the adhesion, and before introduction it is tested again and brought to a cherry-red glow. After permitting the cautery to cool, the trocar is withdrawn, thus allowing the pneumothorax to equalize itself with atmospheric air. The cautery is then introduced through the cannula and observed through the thoracoscope. (Figure 10). Keeping in mind the location of the adhesion to be burned, the tip of the cautery is kept in the field of vision of the thoracoscope, while the eye-piece of the latter is rotated so as to bring the adhesion into view.

The cautery is then placed upon the adhesion which is now tested for sensation. This manoeuvre gives valuable information as to whether the pleura covering the adhesion is reflected from the lung or the chest-wall, as only the latter has sensory-nerve fibres. If the adhesion is broad, it may be lifted with the tip or shaft of the cautery and examined for blood-vessels underneath. In proceeding to cauterize the adhesion, one should bear in mind that the closer the burning is to the chest-wall the greater will be the pain and the danger of bleeding, inasmuch as sensation comes from the intercostal nerves and the blood-supply is derived collaterally from the intercostal vessels. On the other hand, burning near the lung, while painless, is dangerous, because one may burn into a small cavity projecting within the adhesion, or into the lung, and thus liberate infection which is almost certain to result in empyema. Generally speaking, the cauterization should be made where the adhesion is the thinnest.

If the patient's stereoscopic films before operation show a short adhesion, a careful examination should be made to determine whether the adhesion contains an elongated cavity. Cases of this character should be burned as close as possible to the chest-wall, which is likely to be painful and sometimes dangerous because of the possibility of bleeding. However, pain can be controlled by infiltrating the chest-wall attachment with novocaine-suprarenin under thoracoscopic guidance.

The cauterization should proceed slowly and cautiously. If blood-vessels are seen, they should be thrombosed with the flat surface of the cautery before cutting. (Figure 11.) Should bleeding occur, it is stopped at once by the application of the heated cautery or by radiating heat from it. While the tip of the cautery may be in a safe situation and in full view, the operator should see to it that the cautery-shaft, which is not in view, is not resting upon the lung or other important structures which might be damaged by its heat. He should also avoid cauterization in close proximity to large blood-vessels or nerve-trunks, as radiating heat may result in phlebitis or vascular thrombosis, or painful neuritis or shock, if one works too near the sympathetic trunk.

The beginner will do well to confine himself to string- and band-adhesions and avoid diffuse folds. It must be a fixed rule never to burn any tissue until all surfaces have been seen, and no tissue should be cauterized unless the operator is perfectly familiar with its structure. In this way accidents will be avoided. Prolonged cauterization should never be practised, and the cautery-shaft should be allowed to cool at frequent intervals. In addition to the dangers referred to above, I am certain that radiating heat from the cautery is an important factor in the formation of exudate and occurrence of postoperative pain.

The cauterization of large adhesions often gives rise to much smoke inside the pneumothorax space which obscures the visual field. If such is the case, the thoracoscope should be removed and the cannula substituted. The patient is instructed to take a few deep breaths, whereupon air will be sucked in during inspiration and smoke forced out on expiration. If the lens becomes smeared with exudate or blood, the thoracoscope must be removed and wiped clean.

After the adhesion is completely cut through, a careful search should be made, first of the chest-wall stump for bleeding vessels, and then of the lung stump. Any oozing should be stopped by application of the cautery. Bleeding is much less likely to occur from the lung-stump than from the chest-wall stump, as it will be observed that the lung-stump contracts after cauterization to less than half its size before cauterization. (Figure 18–*4*.)

Cauterization with the galvanocautery has many shortcomings from the standpoint of heat and character of cutting. It has been shown that tissue is destroyed for a very short distance around the cautery; blood-vessels are destroyed, and, unless a very dull red heat is used, bleeding may occur. This makes the operation at times tedious. I have over-

come these objectionable features recently by using the electrothermic method, utilizing for this purpose the Wappler-Wyeth endotherm with special electrodes which I have designed. (Figure 12.)

Briefly, the cutting effected by the endotherm is not a true cutting but a molecular disintegration of the tissues produced by a high-frequency undamped current, an arc being formed at the point of contact between the tip of the electrode and the tissue. By this method, blood- and lymph-vessels are sealed; no bleeding occurs, and the danger of liberating tuberculous infection from the cut adhesion is infinitely less. There is no radiating heat, the electrode-shaft remaining cool. There is much less pain when cutting near the chest-wall, and the operation is more quickly executed. Although my experience with this new method is limited, I am sure that the electrothermic method overcomes all of the objections of the galvanocautery and will replace the latter method.

After the operation is finished, the cautery and its cannula are removed, and then the thoracoscope, after which the pneumothorax cavity is freed of smoke by inserting a cannula for this purpose. This leaves the pneumothorax at atmospheric pressure, which is desirable, as positive pressure favors emphysema and the tearing of incompletely cauterized adhesions, while negative pressure favors bleeding. After the pneumothorax space has been freed of smoke, the thoracoscope cannula is removed and a deep stitch is made at the site of puncture. The patient should be emphatically warned at this time against coughing. A small roll of one-inch bandage for compression is made over the site of puncture. This is covered with sterile gauze, and the chest is tightly strapped with several strips of three-inch adhesive plaster extending well to the front and back.

The postoperative care consists of absolute bed-rest with the pneumothorax side up. Cough should be controlled during the first forty-eight hours with opiates, if necessary. Bed-rest should be maintained for seven days. Straining at stool and physical effort, including excessive laughter, should be warned against.

The first reinflation after operation is made with carbon dioxide because its use lessens the danger of gas embolism. The time and quantity of gas reinflation will vary with each individual case. It is sufficient if carbon dioxide is introduced within three or four days. If large cavities are present, collapse of the lung should be brought about gradually with small quantities of gas because of the danger of kinking the drainage bronchus, and the consequent retention of sputum in the cavity. (Figure 13.)

Reinflation should be carefully controlled by the X-ray and a film should be made, preferably after every gas injection for the first few times. If the drainage of a cavity is interfered with, it may be necessary to aspirate gas and expand the lung slightly so as to establish drainage, following which frequent fillings with small quantities of air should be carried out until a satisfactory collapse is established and the patient rendered sputum-free.

At times it is surprising how quickly sputum disappears. If sputum is still raised and contralateral-lung sources can be excluded, the collapse should proceed to compression, using positive pressures if necessary. Should anteroposterior films reveal no residual cavity, lateral films should be made, and the pneumothorax carried on energetically until no sputum is raised. (Figures 14 and 15.)

The postoperative course is, as a rule, mild. Elevation of temperature of to 100° or 101°F. usually follows and sometimes lasts a week. In case of string- or band-adhesions up to 2 cm., at times, no reaction takes place, and the procedure is scarcely more objectionable than a pneumothorax puncture.

INDICATIONS

In considering the indications for cauterization, the first requisite is that the case be one in which, after a reasonable length of time, it can be demonstrated that adhesions are preventing satisfactory collapse of the lung, and recovery is doubtful with a continuation of the partial pneumothorax. There should also be reasonable assurance that the patient will recover, provided a satisfactory collapse is established. In other words, there must be an absence of any serious complication such as extensive disease in the contralateral lung or the intestines, which would probably prevent the patient's recovery even if a satisfactory pneumothorax were established.

Further indications are, first, unsatisfactory pneumothorax on account of incomplete collapse of the lung because of strings, bands, and folds of adhesions; second, satisfactory pneumothorax in spite of adhesions, when high intrathoracic pressure is necessary to maintain the collapse, with consequent danger of lung rupture, and when pressure is furthermore causing uncomfortable symptoms, such as phrenic dyspepsia, coughing paroxysms, and so forth; third, satisfactory pneumothorax in which bands of adhesions have become organized, causing early expan-

sion of the collapsed lung in cases in which the pneumothorax has not been maintained sufficiently long.

With reference to the first group of cases, we feel that it is unjustifiable to keep up an unsatisfactory pneumothorax. The cauterization of adhesions should be considered, if, after a few months of trial, the twenty-four-hour quantity of sputum, after perhaps a preliminary fall, remains more or less stationary, and X-ray study shows that satisfactory collapse of the lung is prevented by adhesions of a reasonably suitable type for cauterization. We formerly used to resort to high intrathoracic pressure, hoping to stretch the offending adhesions. This practice was occasionally successful, but after long experience and study of our end-results we are convinced that this procedure is inadvisable. We believe it better to employ the cautery, if possible; otherwise, utilize other collapse measures, either in conjunction with the pneumothorax or by converting the pneumothorax into an oleothorax and carrying out such other compression procedures as partial or complete thoracoplasty after phrenicotomy, or abandoning the pneumothorax and doing a complete thoracoplasty. Figures 16 to 29 illustrate cases of this type.

The second group of cases comprises those in which the intrathoracic pressure necessary to maintain collapse of the lung causes downward pressure upon the liver and stomach or uncomfortable mediastinal displacement. These patients frequently complain of nausea and anorexia, and either lose weight or fail to gain. In other cases traction of adhesions upon the lung provokes annoying paroxysms of coughing. After cauterization of such adhesions, less frequent refills of gas will be required and the necessity of high intrapleural tension with its dangers will be done away with; it will also relieve pressure upon the liver, stomach and mediastinum. An example of this type of case is shown in figures 30, 31 and 32.

The third group of cases is also commonly met with by those engaged in pneumothorax work. Not infrequently bands of adhesions become organized and contract, and pull out a lung which has had a good collapse. This is often followed by expansion of the lung with recurrence or increase of expectoration, and sometimes haemoptysis. Our policy in these cases is to cauterize these strings or bands and establish a good pulmonary collapse, and then convert the pneumothorax into an oleothorax which prevents further expansion of the lungs. Figures 33, 34 and 35 illustrate a case of this type.

If cauterization is contemplated, it should be done early, before ad-

hesions become organized and collateral circulation is established, and before bronchogenic extension of disease takes place to the same or the contralateral lung.

CONTRAINDICATIONS

Tuberculous disease in the contralateral lung is no contraindication *per se* for the cutting or cauterization of adhesions that prevent satisfactory collapse of a lung. Even a pneumothorax on the contralateral side is no contraindication, provided the indications for bilateral pneumothorax exist. Obviously, the contraindications are the same as those for a satisfactory pneumothorax. The presence of benign exudate is no contraindication, as will be noted later. Cauterization should not be done during an acute formation of exudate. Acute pyothorax contraindicates cauterization, but chronic afebrile pyothorax is not a contraindication *per se*. If, however, there is profuse purulent exudate, it will be found that the adhesions are so covered with fibrin and purulent debris that the nature of tissue to be burned is difficult to determine.

Serous exudate should be aspirated before cauterization is attempted, and in case of purulent exudate one should try to clear up the infection by oleothorax treatment and then aspirate the oil of gomenol before operation. If only a small quantity of purulent exudate is present, the pneumothorax should be thoroughly washed out with normal salt solution before cauterization is attempted. We have cauterized two chronic afebrile cases with purulent exudate, and without unfavorable result. However, we have limited our operations to string- and small band-adhesions. The strictest care must be taken in these cases to prevent infection of the puncture wounds through the chest-wall which may terminate in thoracic fistula. We routinely introduce 150 to 250 cc. of 2.5 to 5 per cent oil of gomenol in all cases in which purulent exudate was present before operation, or when we encounter tuberculous changes in adhesions during their cutting, or when caseous tubercles are seen on the visceral or parietal pleura. We are convinced that this precaution lessens the danger of infection.

SELECTION OF CASES

The selection of cases for cauterization should be made only after a careful study of, preferably, stereoscopic X-ray films taken before the pneumothorax and during its entire course. Stereoscopic-film study is obligatory before operation, in order that one may be perfectly informed

as to the position of cavities in the collapsed lung and their probable relation to adhesions, as well as the location of adhesions and their attachments to the lung and chest-wall.

A careful record of the influence of the pneumothorax on the twenty-four-hour quantity of sputum, as measured at weekly or monthly intervals, should be available. If the original film shows a superficial cavity, and serial films during the evolution of the pneumothorax show short adhesions holding the lung close to the chest-wall, it may be suspected that the adhesion contains a prolongation of the cavity or lung tissue, and cauterization would be dangerous. In the case of large cavities, the floor of the cavity is not infrequently mistaken on X-ray films for a band-adhesion, the cauterization of which would certainly be followed by bad results. (Figure 36.) Here a study of the quantity of sputum, and of the original films and stereoscopic films of the pneumothorax will serve as a useful guide. (Figures 37 and 38.) In case of doubt, 20 to 40 cc. of lipiodol may be injected into the pneumothorax space, and the patient examined under the fluoroscope in various positions that favor gravitation of the lipiodol to the upper part of the pneumothorax cavity. In case one has to deal with the wall of a cavity, the position of the lipiodol shadow and the inability of the lipiodol to pass behind or in front of the barrier will clearly indicate the nature of what was thought to be an adhesion. An example of this type of case is shown in figure 39. This patient was referred for cauterization of what was thought to be a band-adhesion extending from the collapsed lung to the chest-wall. (Figure 39–*2*). Study of the patient's sputum showed its reduction in quantity to be inconsistent with the apparent collapse; for, in spite of prolonged pneumothorax and a fair collapse shown on the single film, the quantity of sputum remained nearly the same, and the contralateral lung could be excluded as a source of sputum. While the film suggested a band between the partially collapsed lung and lateral chest-wall, clinical study was convincing that the cavity had been uninfluenced by the pneumothorax, and that what was formerly interpreted as a band-adhesion must be the floor of the cavity.

Lipiodol was injected into the pneumothorax space, and its movement noted under the fluoroscope as the patient was tilted, head down, on the table. This examination confirmed the opinion that what was thought to be a band-adhesion was the floor of the cavity, as it was impossible for the lipiodol to flow in front of or behind the obstacle. (Figure 40.) Thoracoscopic examination confirmed this opinion.

A careful study of stereoscopic films should be made before cauterization, but not too much dependence placed upon it, for at times one is perfectly amazed at the number of adhesions, which are not shown on stereoscopic films, but are to be found on thoracoscopic examination. In nearly every instance, one encounters adhesions not visualized by the most careful roentgenological technique.

Frequently, adhesions not shown on X-ray films are technical factors preventing collapse of the lung. I refer to string-adhesions as tough as catgut and scarcely any larger, extending from the partially collapsed lung to the chest-wall, and sometimes giving the partially collapsed lung a tented contour. In one of our cases, in which there was supposedly only a small band-adhesion present, we encountered a half-dozen slender strings of the type referred to above,—too fine to be shown on the X-ray film, and collapse of the lung did not take place until they were cauterized.

Not infrequently what appears to be a band-adhesion on stereoscopic films proves to be a diffuse fold-adhesion with a thick edge. (Figure 41.) Undoubtedly, the most valuable method of determining the possibility of cauterization is by thoracoscopic examination of the pneumothorax cavity, and in any doubtful case this procedure should be utilized, inasmuch as it is harmless.

RESULTS

During the past three years we have done 100 cauterization operations with the results shown in table 2. The results of the operation have to do with its immediate result and not the end-result of the pneumothorax, as that has no bearing on the operation, but is subject to the various factors which influence pneumothorax therapy. However, every case classified as *clinically and technically successful* means that complete cauterization of all adhesions followed by a satisfactory pneumothorax with prompt, sometimes immediate, disappearance of fever, cough and expectoration, was attained.

It will be noted that the greatest success was achieved in the string and band type of adhesions. The string-adhesions were from approximately 0.5 to 2 cm. in diameter and essentially round. The band-adhesions here dealt with were from 0.25 to 2 cm. thick, and 2 to 10 cm. wide.

Adhesions in the form of folds with broad bases are commonly met with between the apex of the lung and the dome of the thorax, as well as along

the posterior wall of the pneumothorax space, extending from the lung around the costovertebral gutter to the lateral aspects of the chest-wall. Adhesions of this type frequently look like bands on stereoscopic films. Our technical and clinical successes have been much fewer in cauterizing this type of adhesion. One can cautiously cut the free edge toward its base (figure 42, *1–2*) and, as shown in our results, sometimes secure a technically and clinically successful result. Our technically and clinically unsuccessful cases were entirely of this type.

TABLE 2

Intrapleural pneumolysis: Jacobaeus-Unverricht method: 100 cases

RESULTS OF OPERATION	NUMBER OF CASES	FOLDS	STRINGS AND BANDS	TOTAL PERCENTAGE OF CASES
Technically and clinically successful (satisfactory pneumothorax immediately, with disappearance of cough and expectoration)	63	6	57	63
Technically unsuccessful, clinically successful: incomplete cauterization	11	11		11
Total: Clinically successful	74	17	57	74
Technically successful, clinically unsuccessful: bilateral pneumothorax	1		1	1
Technically and clinically unsuccessful	25	25		25
Examined with thoracoscope and found unsuitable for operation (referred cases)	13	13		
Dead: Due to independent evolution of disease, as in other lung, intestines, etc., not related to operation	6			

In our series of 100 cases, there were 14 single string- or band-adhesions. In 44 cases there were multiple strings and bands, and in 42 cases diffuse folds. The diffuse-fold type of cases should not be attempted until one has had considerable experience with the method.

In 92 of our cases, a single cauterization operation was done, and 68 were successful and 24 unsuccessful. These latter were all cases with the diffuse-fold type of adhesions. In 4 cases two cauterizations were done, three of which were successful and one unsuccessful because of the presence of diffuse folds. In two cases, three cauterizations were performed with a successful end-result in each. Two cases were operated upon four times each. A satisfactory collapse was obtained in one; the other experienced improvement in the collapse but diffuse folds of adhesions prevented a satisfactory end-result.

In the case of single or multiple string-adhesions, one cauterization will usually suffice, but with multiple band-adhesions and folds it is often necessary to do repeated cauterizations. The following is a very interesting case of this kind:

Case 6093: (Figure 43): Female; age 24 years; sick one year. Physical and roentgenological examination revealed fibrocaseous tuberculosis with cavity, involving two-thirds of the right lung and with bronchogenic disseminations in the contralateral lung.

The average 24-hour quantity of sputum was 40 cc. Tubercle bacilli positive. Temperature range 100° to 101°F. in the afternoon. Weight 110 lbs.

A very gradual collapse of the right lung was instituted in spite of the disease on the contralateral side. At the end of a month the patient's general condition was improved. She had gained 3 lbs. in weight; her temperature ranged under 100°F.; but her sputum, after a preliminary fall the first two weeks to 25 cc. in 24 hours, remained stationary the following month in spite of larger gas refills and increasing intrapleural pressure. The contralateral lung showed no progressive changes.

Stereoscopic films of the pneumothorax at the end of six weeks (figure 44) revealed at least two cavities (*5* and *6*) held open by multiple string- and, probably, band-adhesions (*1*, *2*, *3* and *4*) extending from the partially collapsed lung to the dome of the pneumothorax space, particularly posteriorly, but some also anteriorly.

In order to secure a better collapse of the lung, cauterization was decided upon. Thoracoscopic examination, through a posterior approach, disclosed numerous strings and bands not shown upon the stereoscopic films. One large band (Figure 44–*1*), extending from the apex to the dome of the pneumothorax space, was cut, as were several string-adhesions (figure 44–*4*), all of which seemed of technical importance.

Other strings and bands were seen anteriorly, and apparently a fold extending from the lung across the costovertebral gutter to the posterolateral aspects of the chest-wall. The anterior string-adhesions did not seem to be of sufficient importance to prolong the operation, and the fold posteriorly seemed insignificant. However, in spite of the cauterization of several adhesions of importance, the 24-hour quantity of sputum remained essentially the same, although stereoscopic films (figure 45) showed the apical band had been cut and one cavity (*5*) was much smaller. Other small string-adhesions were also shown to have been cut.

A second cauterization anteriorly was decided upon, as it seemed probable that the strings of adhesions anteriorly were of greater significance than at first estimated. Accordingly, the thoracoscope was introduced anteriorly in

the second intercostal space in the midclavicular line. A good view of the pneumothorax was obtained, and again two string-adhesions, which alone seemed of technical importance, were cut. There was also seen, at this time, the fold of pleura extending upward from the collapsed lung across the costovertebral gutter, but it was not even at this time considered of technical importance. Besides, it had all the appearance of an unapproachable fold. Moreover, it was felt that the two remaining string-adhesions, shown in figure 45 at *2* and *3*, had been severed. However, much to our surprise, stereoscopic films after the second cauterization revealed no essential changes in the pulmonary collapse. (Figure 46.) Apparently what had been considered an insignificant fold, when viewed at a distance during the two previous operations, was a structure of greatest technical importance.

While, upon thoracoscopic examination, the offending structure appeared to be a fold, it had the appearance of two bands on stereoscopic films. Accordingly, to determine whether it was a fold of pleura which probably could not be safely cut, or a band-adhesion which could be cut without danger, 20 cc. of lipiodol was injected into the pneumothorax cavity. The patient was placed recumbent upon the fluoroscopic table, and the head of the table was slowly lowered so that the movement of the lipiodol could be noted. It was seen to flow slowly toward the adhesion, and then penetrate it near the middle, and then appear above it. (Figure 47.) By rolling the patient, the lipiodol (figure 47–*1* and *3*) was made to surround the attachment of the adhesion to the chest-wall (figure 47–*2*), which appeared as an irregular area of lessened density amid the opaque shadow of the lipiodol.

Upon elevating the head of the table the lipiodol above the adhesion was seen to flow back through the opening into the pneumothorax cavity below. We were thus convinced we had to deal with a fold-adhesion, that had a small opening posteriorly and extended from the lung over the uncollapsed cavity across the costovertebral gutter, and was attached to the chest-wall between the 6th and 8th ribs in the scapular line.

Accordingly, a third attempt was made to secure collapse of the lung. To accomplish this the thoracoscope was introduced through the 7th intercostal space in the scapular line. Upon thoracoscopic examination the adhesion (figure 48) had every appearance of a fold of parietal pleura without any opening beneath. However, exploration with the author's blunt electrode brought to light the opening (figure 49) through which the lipiodol had been seen passing. As numerous blood-vessels were present, electrocoagulation with the blunt electrode and bipolar current was first done. The adhesion was then cut (figure 50) with the endothermic electrode without any bleeding whatever, and a satisfactory collapse of the cavity followed immediately. (Figure 51). The patient's sputum was reduced to 3 cc. within one week after the cauterization.

It is always advisable to avoid prolonged cauterization, although one to two hours may be borne very well by the patient if one proceeds slowly, and interrupts the operation frequently in order to let the cautery cool if the galvanocautery is used. During these intermissions the light of the thoracoscope should be shut off.

Prolonged cauterization is undesirable because of reactions caused by chemical changes which tissue proteins undergo at the site of cauterization, and also because of the effect of radiating heat from the cautery upon the pleura and other anatomical structures. This danger is strikingly brought out in

Case 6172: (figure 52): Female; sick one and one-half years. The physical and roentgenological examinations revealed a fibrocaseous tuberculosis, with cavity, involving the upper half of the right lung, and perihilar infiltration on the contralateral side. The patient's sputum averaged 33 cc. in 24 hours and was positive for tubercle bacilli.

Pneumothorax treatment was instituted, but after 5 weeks, in spite of constantly increasing amounts of air on refills, the sputum was reduced to only 30 cc. in 24 hours and the intrapleural pressure became positive. While stereoscopic films revealed no evidence of adhesions (figure 53) the lung was not collapsed as much as one would expect, considering the amount of air injected. Consequently, in spite of the roentgenological findings, adhesions were suspected of interfering with the collapse of the lung.

Stereoscopic film study at this time (figure 54), after a large refill of gas, showed a string-adhesion extending from the upper lobe to the lateral chest-wall. Of greater importance, however, was an adhesion attached near the sternal end of the first rib, and passing downward, backward and inward to the partially collapsed apex of the right lung. Thoracoscopic examination confirmed our roentgenological impression regarding the location of the adhesion. The lower adhesion extended from near the interlobar fissure between the upper and lower lobes of the right lung to the posterior lateral chest-wall. (Figure 55.) The apical adhesion, however, was a fan-shaped band with its broad base attached to the chest-wall. The most suitable place for cutting the adhesion lay only 2.5 cm. distant from the superior vena cava. (Figure 56.) Along the upper border of the adhesion a faint blue line was observed, extending from the chest-wall to the lung. This had somewhat the appearance of a large vein or a slender linear area which at a distance might be confused with a vein. The author's blunt electrode renders a very useful purpose in differentiating such structures, as the blunt end of the electrode permits the exploration of adhesions without the danger of injury to tissue. Thin areas on adhesions are transparent, whereas veins are not. (Figure 57.) If the structure had proved

to be a vein, one was in a position to obliterate it by electrocoagulation before cutting.

The possibility of heat from a galvanocautery damaging the vena cava when in such close proximity seems worthy of consideration, and supports our contention that the endotherm will replace the galvanocautery because of the essential absence of heat and the possibility of using a cutting or coagulation current in the endothermic outfit. Figure 58 is a thoracoscopic view of the adhesion cut by the endothermic method, and figure 59 is a film taken immediately after the operation.

In the case of multiple adhesions, if extensive, it is always well to cauterize those which seem, on thoracoscopic study, and with the stereoscopic image in mind, to be of technical importance. A careful check can be made by the X-ray after refills, and subsequent operations may be undertaken at weekly or monthly intervals, as the case demands.

Clinical success is not dependent upon the cauterization of all adhesions. Even apical adhesions do not always require cauterization, if sufficient horizontal collapse can be obtained, except in the case of superficial apical cavities when collapse is prevented by apical adhesions alone, or in cases in which vertical collapse of the lung is also necessary.

In instances of multiple adhesions attached to the lateral aspects and dome of the pneumothorax space it is often advisable to cauterize the lateral adhesions first, thus permitting more traction upon the apical ones, as frequently these are sufficiently stretched to render a second cauterization at a later date a much less dangerous affair. But in many instances a second cauterization will be found unnecessary. (Figures 60, 61, 62 and 63.)

In most cases innocent adhesions may be seen extending from the lung to the costovertebral gutter posteriorly, and anteriorly to the region of the sternum. Because of their proximity to large vessels and nerve-trunks these should not be molested unless there is unquestionable evidence that their presence is preventing satisfactory pulmonary collapse.

Adhesions attached to the lateral chest-wall offer no difficulty. Those extending from the apex of the lung to the dome of the thorax, while not technically difficult to cauterize, should be approached with timidity if they are short, and require cauterization near large blood-vessels or in proximity to the brachial plexus.

Diaphragmatic adhesions also offer no particular difficulty, according to our experience, and their cauterization is painless. If, however, they are extensive they should be let alone and a phrenicotomy performed.

COMPLICATIONS

We have had no serious accident (table 3). In 42 cases serous exudate was present at the time of operation, but in no instances were the quantities of fluid large. In cases with fluid the reaction to operation was no different than in those without fluid, except that, on the whole, more fluid occurred after operation than in the fluid-free cases. However, the end-result was in no instance impaired, nor was the postoperative course more stormy than in those without fluid at the time of operation.

Of the 58 cases without fluid before cauterization, 48 developed fluid after operation. In 28 of the latter it was moderate and required no aspiration, while 20 cases were aspirated and treated as cases in which fluid occurred during the course of pneumothorax. Purulent exudate

TABLE 3

Complications before and after operation in 100 cases

Serous exudate	Before operation, 42	Developed after operation, 48
Purulent exudate (tuberculous)	Before operation, 2	Developed after operation, 16
Purulent exudate (nontuberculous)	Before operation, 0	Developed after operation, 0
Haemorrhage (moderate; easily controlled by cautery), 1		
Severe reactions (high fever, etc.), 7		
Shock or serious operative complications, 0		

was present before operation in two cases, but it was not aggravated by cauterization. Sixteen cases developed empyema; all of them were tuberculous. In one case developing purulent exudate large conglomerate subpleural tubercles were seen in the lower lobe of the lung on thoracoscopic examination. Three cauterizations of apical adhesions were done at invervals of two weeks to a month. Three months after the last cauterization, empyema developed, and was treated with injections of oil of gomenol. The patient coughed up the gomenol when in a sitting position only, at which time the site of spontaneous rupture of the caseating tubercles in the lower lobe was submerged in the gomenol. It is our opinion that the empyema was in no way caused by the cauterization, but was due to the independent evolution of preëxisting disease.

In three of the 16 cases developing empyema tube-drainage was re-

sorted to; in nine the empyema cleared up under oleothorax, and four cases are still under oleothorax treatment but are doing satisfactorily. Tuberculous empyema was predicted in 7 cases before we resorted to oleothorax because during the cauterization scattered caseous tubercles were encountered in the adhesions. All of these were ordinary fold types.

It is our routine to place 150 to 250 cc. of 2.5 to 5 per cent oil of gomenol in the pneumothorax cavity after cauterization in cases in which pleural tubercles are seen and empyema is anticipated. We believe that it has had a very beneficial influence in preventing disseminated infection. We have had no empyema due to pyogenic bacterial infection. Bleeding to the extent of a few drops was frequently encountered in band and fold types of adhesions, but it either stopped spontaneously or was controlled by the cautery. Moderate haemorrhage occurred in one case (2 litres), but it was easily controlled by cauterization after the bleeding point was found; in this case multiple band-adhesions were cauterized. No bleeding occurred in any case with string-adhesions. Severe febrile reactions occurred in 5 cases. In one instance the fever lasted three weeks, and in two others less than ten days. No shock or other serious complications were observed. Slight subcutaneous emphysema sometimes occurs, when it is usually the result of uncontrolled cough or light strapping after operation.

COMMENT

This paper deals almost exclusively with the cauterization of adhesions according to the method of Jacobaeus, utilizing Unverricht's thoracoscope. However, our limited experience with the endothermic method has been so gratifying that recently we have adopted it routinely.

The details of the technique of cutting adhesions by the endothermic method is, in general, essentially the same as those for galvanocauterization, except that the underlying electrical principles involved are entirely different and require a thorough knowledge of the current being used, as well as other important particulars which will be communicated fully in a later publication.

The technique of cauterization of adhesions by the Jacobaeus-Unverricht method is simple and free from danger. The operator should be thoroughly familiar with the appearance of the pleural cavity and as thoroughly trained in the manipulation of the instruments with either hand. This training may be secured by inducing pneumothoraces on

tuberculous cadavers. For practice, I suggest a model of the human lung covered with a bird cage. Strips of paper may be pasted between the lung and cage to imitate adhesions, and the cage then covered with heavy paper. The thoracoscope and cautery are introduced, and practice exercised in approaching and burning adhesions running in any direction. The operator should be perfectly familiar with the distance of structures viewed through the thoracoscope. It is well to remember that what appears to be 1 cm. wide, if 1 cm. distant from the lens of the Unverricht instrument, will appear 0.2 cm. wide if 5 cm. distant from the lens. The tip of the cautery will serve as a useful gauge. This method of calculation is very important in estimating the size of adhesions and vessels, as well as the proximity of important structures to the point of cauterization.

We are convinced of the value of the Jacobaeus-Unverricht operation, and regard it as a distinct contribution and asset to collapse therapy. While in many cases a satisfactory collapse of the lung can be established in spite of adhesions, we regard attempts to stretch adhesions by high intrathoracic pressure more dangerous and less successful than cauterization. The operation of cauterization is a minor affair to the patient, and, if successful, will convert a useless pneumothorax into a satisfactory one and save the patient from thoracoplasty. The operator requires experience in phthisiology and surgery, and use of the method should be confined to surgeons with a pneumothorax background and experience in tuberculosis or to phthisiologists who have had a surgical training.

PLATE 1

Fig. 1. Short band-adhesion extending from the dome of the thorax to the lung, preventing closure of a large apical cavity

Average quantity of sputum in 24 hours, 60 cc.; tubercle bacilli positive. Pneumothorax one and a half years. No essential reduction in sputum for past year

1: Adhesion

2: Cavity

3: Note marked mediastinal bulging. Continuation of such a pneumothorax is futile

Fig. 2. Same case as fig. 1, one week after cauterization of adhesion

Average quantity of sputum in 24 hours, 15 cc. A typical example of the immediate effect of cauterization of offending adhesions

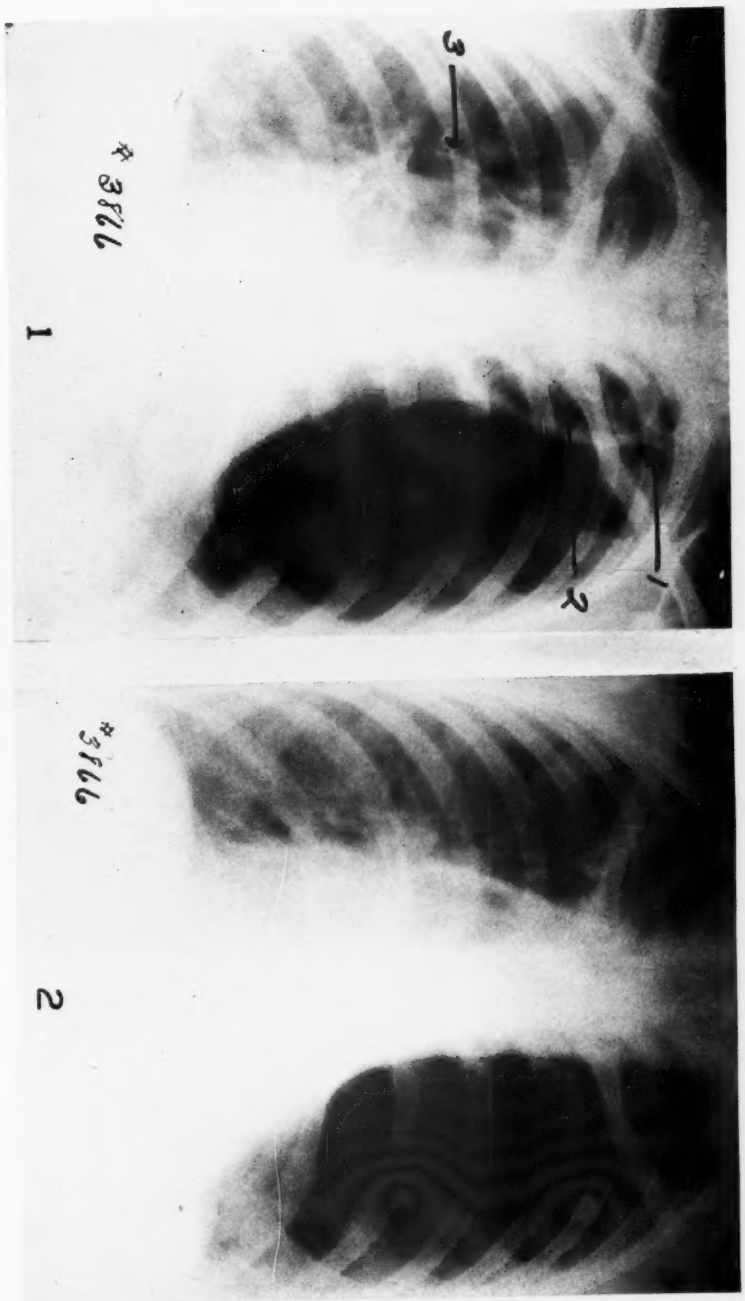


PLATE 1

PLATE 2

Fig. 3. Jacobaeus and Unverricht instruments

1: Unverricht curved cautery

2: Jacobaeus straight cautery

3: Unverricht thoracoscope

4: Jacobaeus thoracoscope (note difference in size)

5: Trocar and cannula with ball-valve for Unverricht thoracoscope

6 and *7:* Jacobaeus trocars and cannulae for thoracoscope and cautery

8: Trocar and cannula for Unverricht curved cautery

9: Trocar and cannula for Unverricht straight cautery (Unverricht now has a flexible cannula for either straight or curved cautery)

10: Cannula for ventilating smoke from pneumothorax

11: Forceps for excising tissue for biopsy

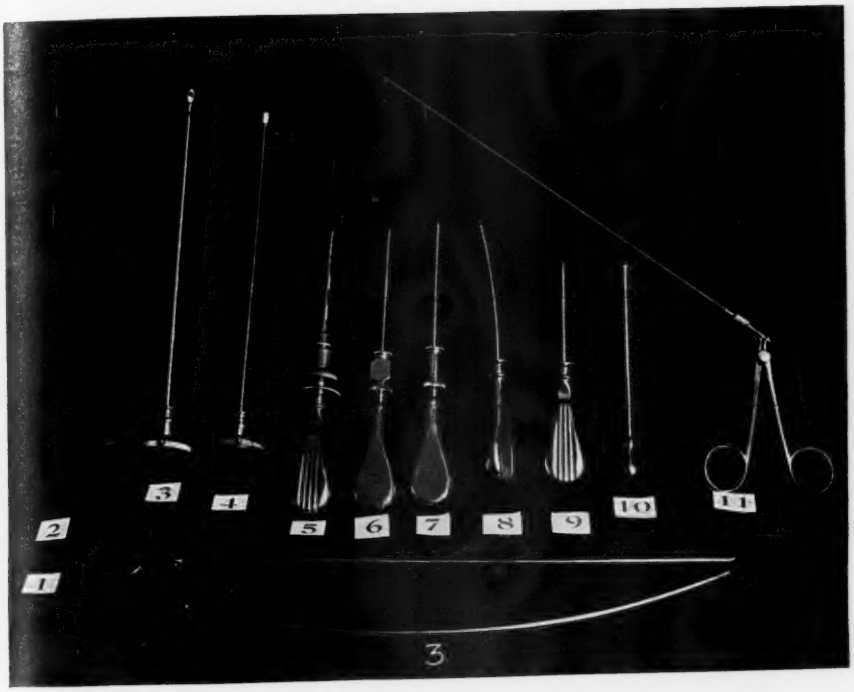


PLATE 2

PLATE 3

Fig. 4. Posterior view of patient draped for introducing the thoracoscope through the posterior chest-wall and the cautery through the lateral chest-wall

Fig. 5. Anterior view of patient draped for operation, as shown in fig. 4

Fig. 6. Introducing the trocar and ball-valve cannula for the thoracoscope through the posterior chest-wall

Fig. 7. Examination of the pneumothorax cavity with the thoracoscope preliminary to introducing the active electrode or cautery

PLATE 3

PLATE 4

Fig. 8. Diagram of pneumothorax with string-adhesion preventing collapse of a cavity, and showing proper position of thoracoscope and active electrode or curved cautery

Fig. 9. Diagram showing partial pneumothorax with broad band-adhesion at base and multiple string-adhesions preventing collapse of two cavities in the lung

The point of entrance of the thoracoscope is proper, but the cannula for the cautery is shown introduced too low, as the broad band-adhesion prevents its visualization through the thoracoscope

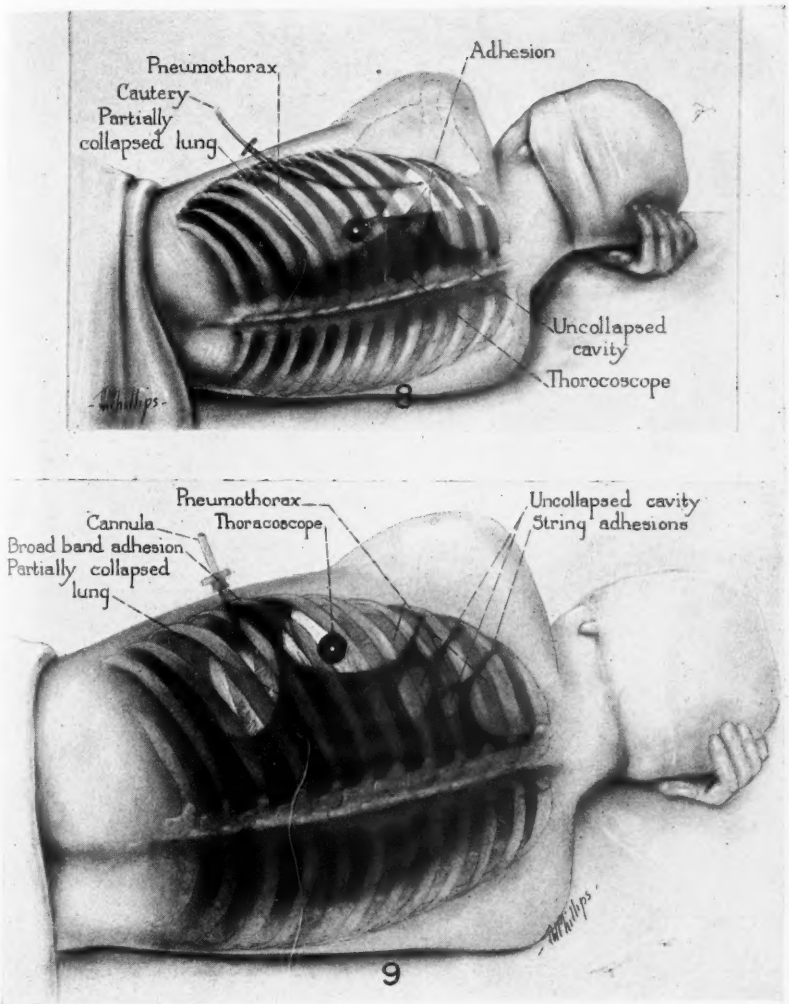

Pneumothorax
Cautery
Partially collapsed lung
Adhesion
Uncollapsed cavity
Thorocoscope
8
Pneumothorax
Cannula
Broad band adhesion
Partially collapsed lung
Thoracoscope
Uncollapsed cavity
String adhesions
9

PLATE 4

PLATE 5

Fig. 10. Thoracoscope and active electrode in position for cutting adhesions in the posterolateral aspects of the pneumothorax

1: Active electrode for endothermic cutting of adhesions
2: Flexible cannula
3: Thoracoscope
4: Ball-valve cannula for the thoracoscope
5: Wappler-Wyeth endotherm

PLATE 5

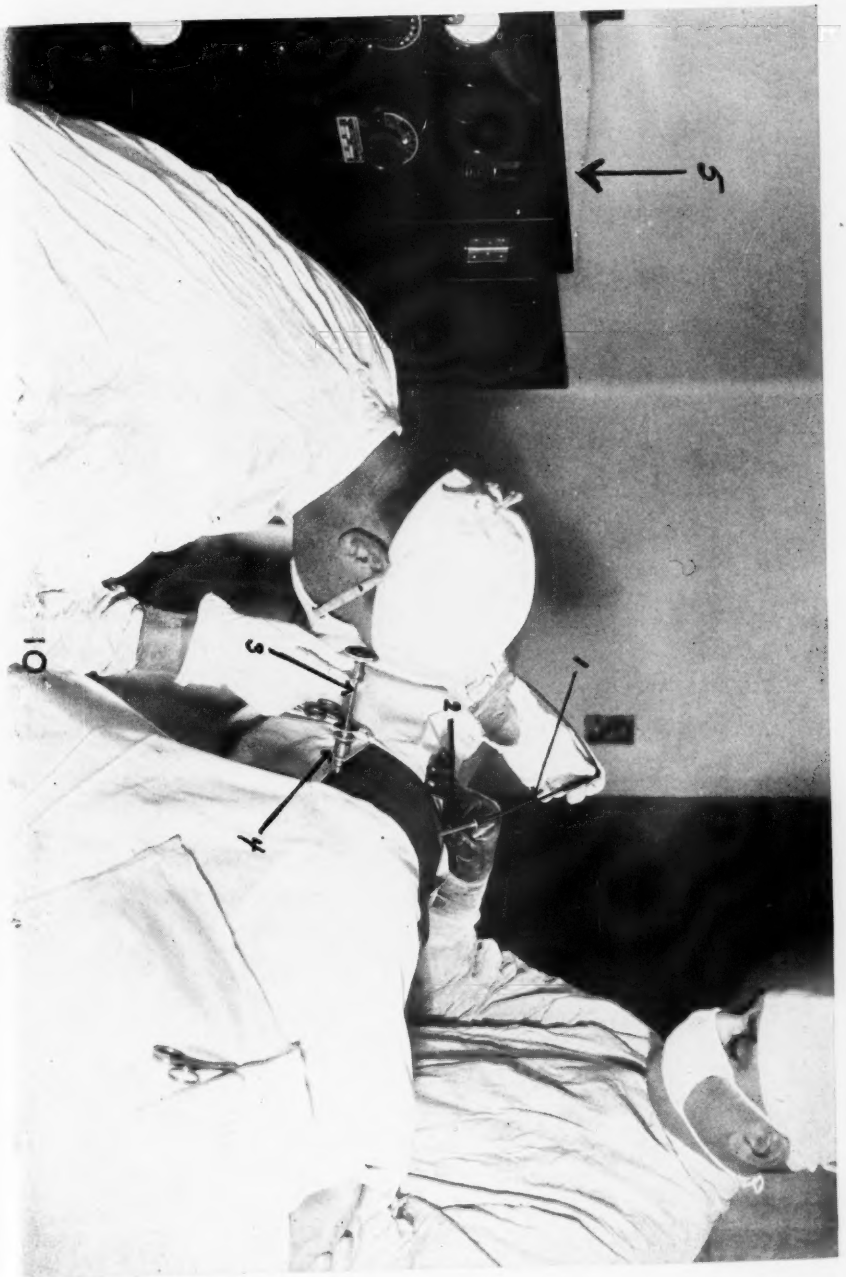


PLATE 5

PLATE 6

Fig. 11. Electrocoagulation of an adhesion before cutting

a: Adhesion

b: Author's cutting electrode, showing application of flat surface through which is passed a high-frequency damped current for the purpose of obliterating blood- and lymph-vessels by electrocoagulation before cutting

c: Electrocoagulation zone

d: Intercostal muscle

e: Rib

f: Fluid in pneumothorax cavity

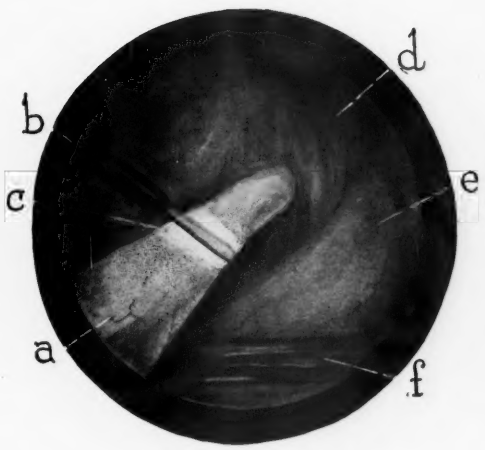


PLATE 6

PLATE 7

Fig. 12. Author's electrodes for cutting adhesions by the endothermic method and for electrocoagulation before cutting

1 and *2:* Curved electrodes

3: Straight electrode

4 and *5:* Blunt electrodes for exploring the nature of folds and large bands and for diathermic coagulation of tissue containing blood-vessels before cutting

6: Trocar for introducing flexible cannula

7: Flexible cannula

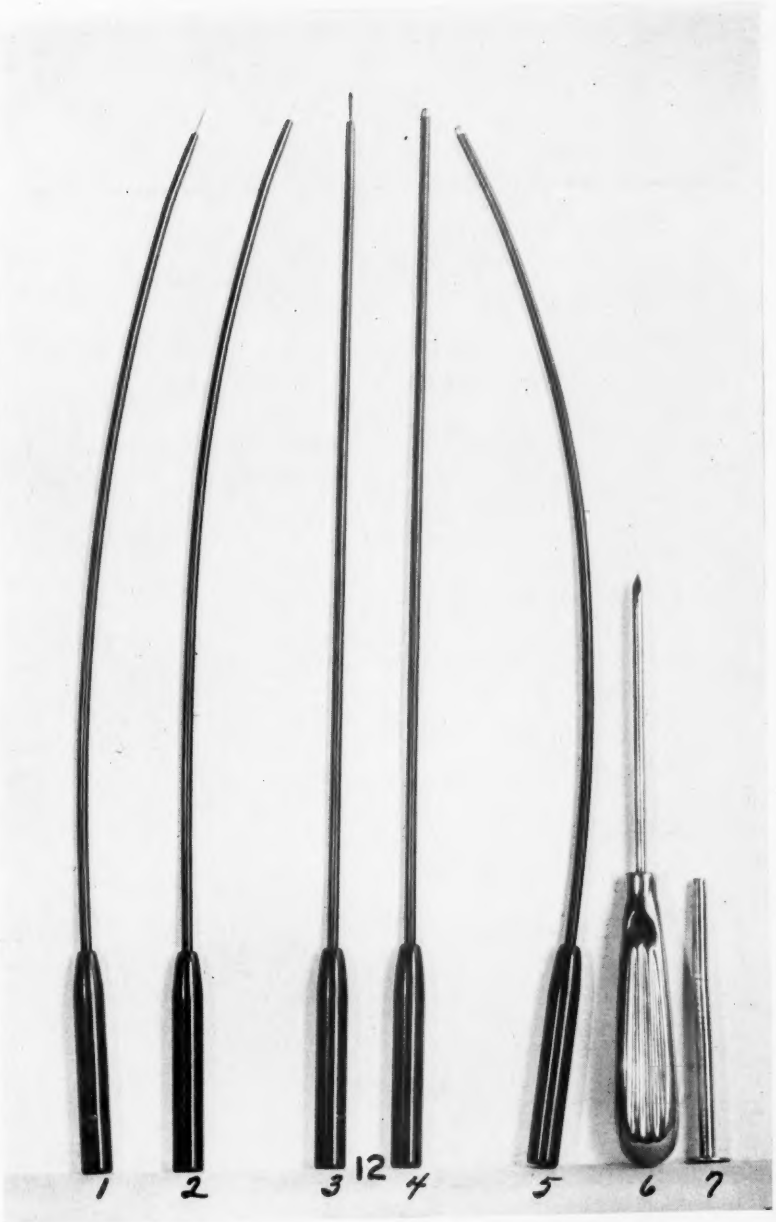


PLATE 7

PLATE 8

Fig. 13. After cauterization of a string-adhesion, too rapid collapse of the lung by large refills of air caused kinking of the drainage bronchus of a large cavity, resulting in retained sputum

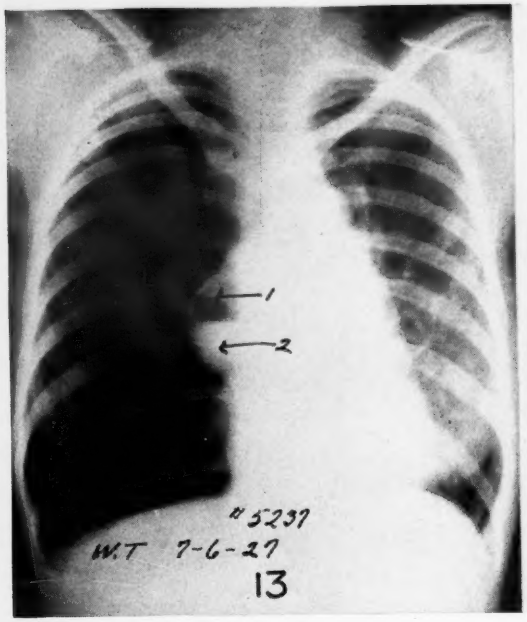
1: Cavity

2: Retained sputum

Fig. 14. Same case as fig. 13. Fifteen days after aspiration of air to slightly expand the lung and establish drainage, followed by small frequent refills of air and gradual collapse. Cavity not visible in anteroposterior position in spite of daily average expectoration of 8 cc. of sputum

Fig. 15. Same as fig. 14. Anterolateral view showing uncollapsed cavity not visualized on anteroposterior films

1: Cavity



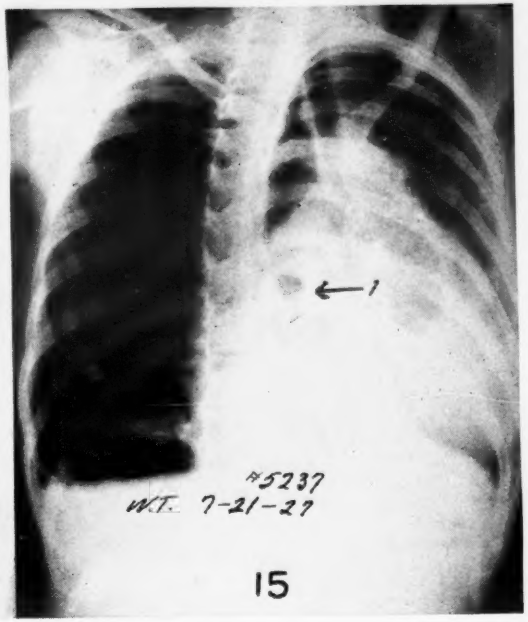


PLATE 8

PLATE 9

Fig. 16. Case 5070. Female; age 21 years; sick eighteen months; pneumothorax three months. Average quantity of sputum in 24 hours, 30 cc., tubercle bacilli positive. Temperature, 100° to 101°F.

1 and *2:* String adhesions

3: Uncollapsed cavity

Fig. 17. Case 5070. Approximately six weeks later. Sputum 25 to 30 cc. in 24 hours, tubercle bacilli positive. Temperature 99° to 100°F. One string-adhesion preventing collapse of cavity (*2*) before cauterization. The other string-adhesion, shown in fig. 16 and not visualized on this film, was found on thoracoscopic examination to have been stretched out into a very slender tenacious string

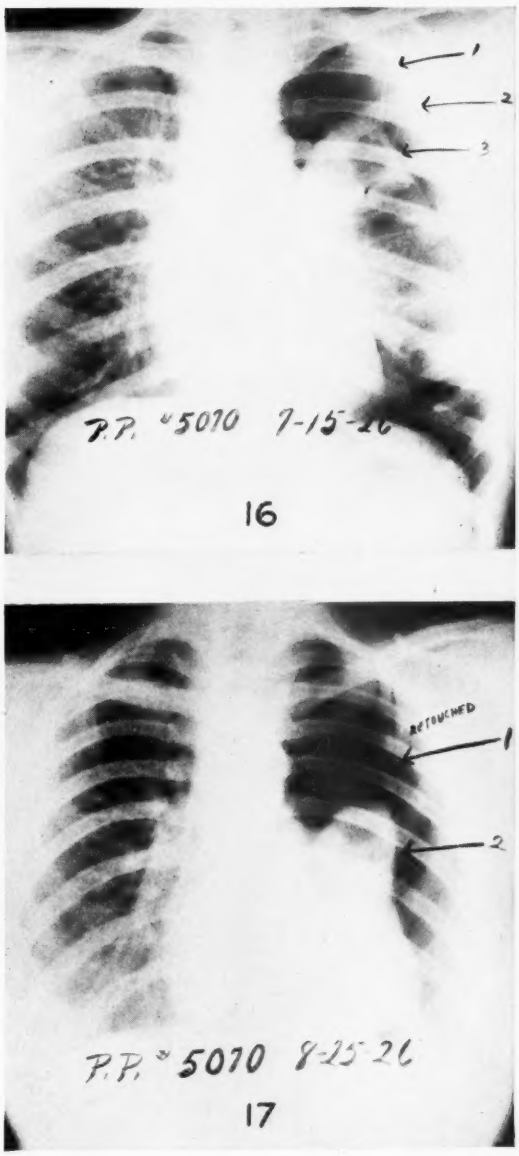


PLATE 9

PLATE 10

Fig. 18. Case 5070

1: Thoracoscopic view of the single string-adhesion shown in fig. 17. *a:* Adhesion *b:* Periosteum of rib. *c:* Internal intercostal muscle

2: Thoracoscopic view of cautery tip (*d*) on adhesion, coagulating the tissue by using the flat surface to obliterate blood-vessels before burning

3: Thoracoscopic view of cutting the adhesion

4: Retraction of the pulmonary stump of the cut adhesion

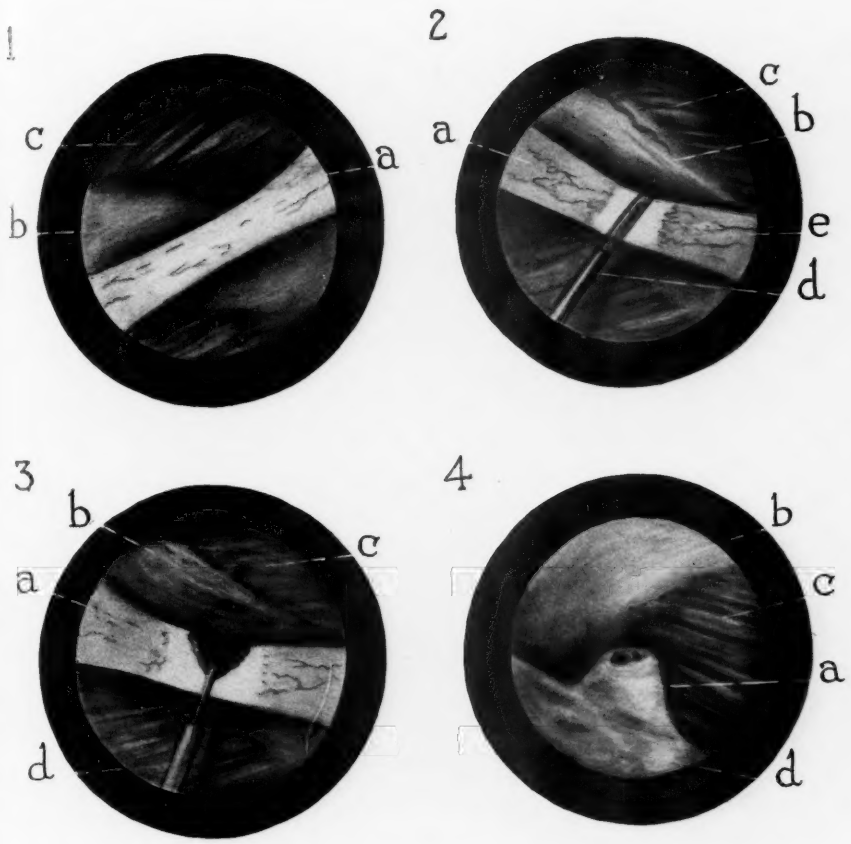


Fig. 18

PLATE 10

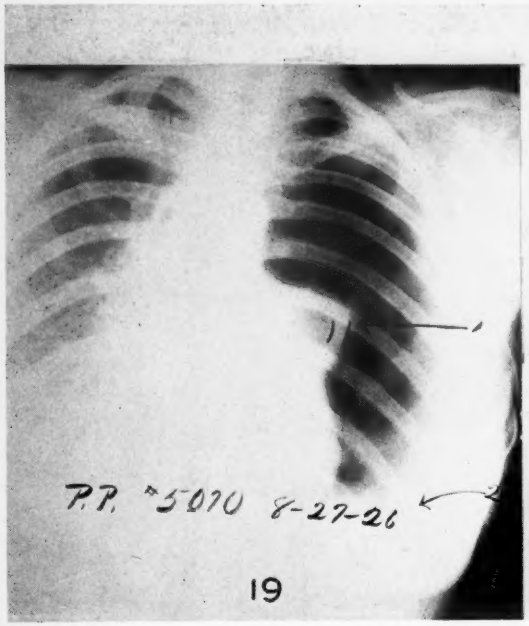
PLATE 11

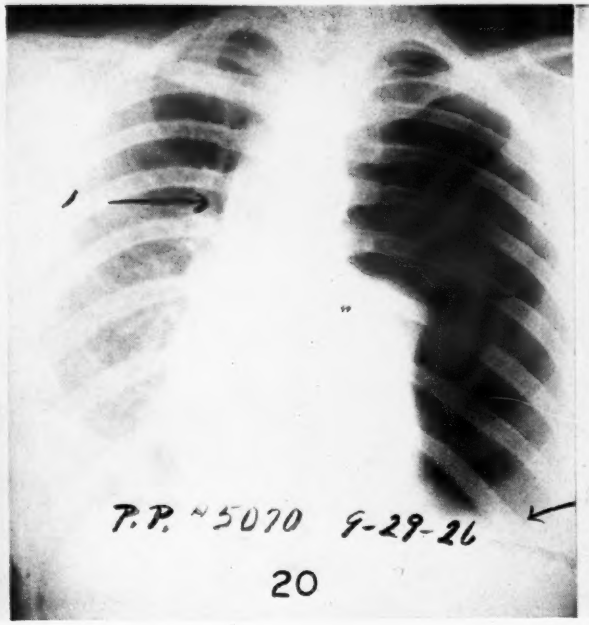
Fig. 19. Case 5070. Two days after cauterization of string-adhesion showing uncollapsed thick-walled cavity (*1*)

Fig. 20. Case 5070. One month after cauterization. Sputum 6 cc. in 24 hours, tubercle bacilli positive. Cavity (*2*) nearly closed

Fig. 21. Case 5070. Nine months after cauterization. Sputum absent for six months. Patient ambulant with satisfactory pneumothorax and without sputum two years and three months later

This is an example of a rigid-walled cavity requiring constant attention to gas refills necessitating gradual collapse. Sputum disappears slowly because of difficulty in collapsing the rigid-walled cavity





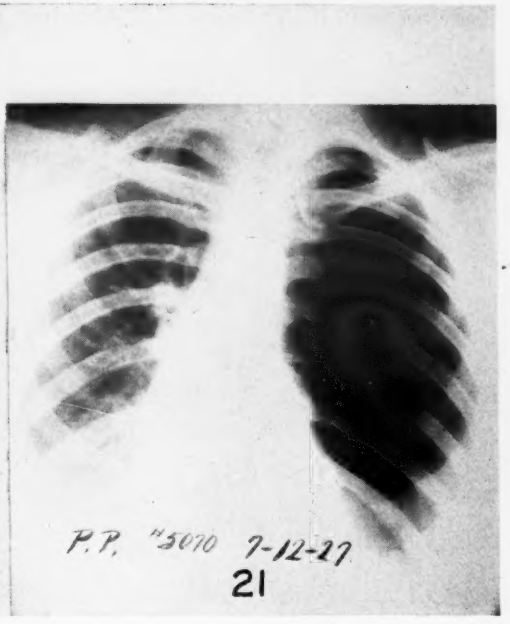


PLATE 11

PLATE 12

Fig. 22. Case 4085. Female; age 18 years; sick five months; loss of weight, 30 pounds; temperature 100° to 101°F.; sputum 30 cc. in 24 hours, tubercle bacilli positive. Large cavity in apex

Fig. 23. Case 4085. One month later with pneumothorax three weeks. Sputum 25 to 30 cc., tubercle bacilli positive; temperature 99° to 100°F.

Fig. 24. Case 4085. Pneumothorax four months. Sputum 20 cc., tubercle bacilli positive; temperature 99.4°F.

1: Band-adhesion at apex

2: Uncollapsed cavity

Cauterization indicated because of stationary quantity of sputum

Fig. 25. Case 4085. Five weeks after cauterization. Sputum 0 to 3 cc., tubercle bacilli negative; gain in weight 8 pounds; temperature normal. Patient ambulant with negative sputum two and a half years since cauterization

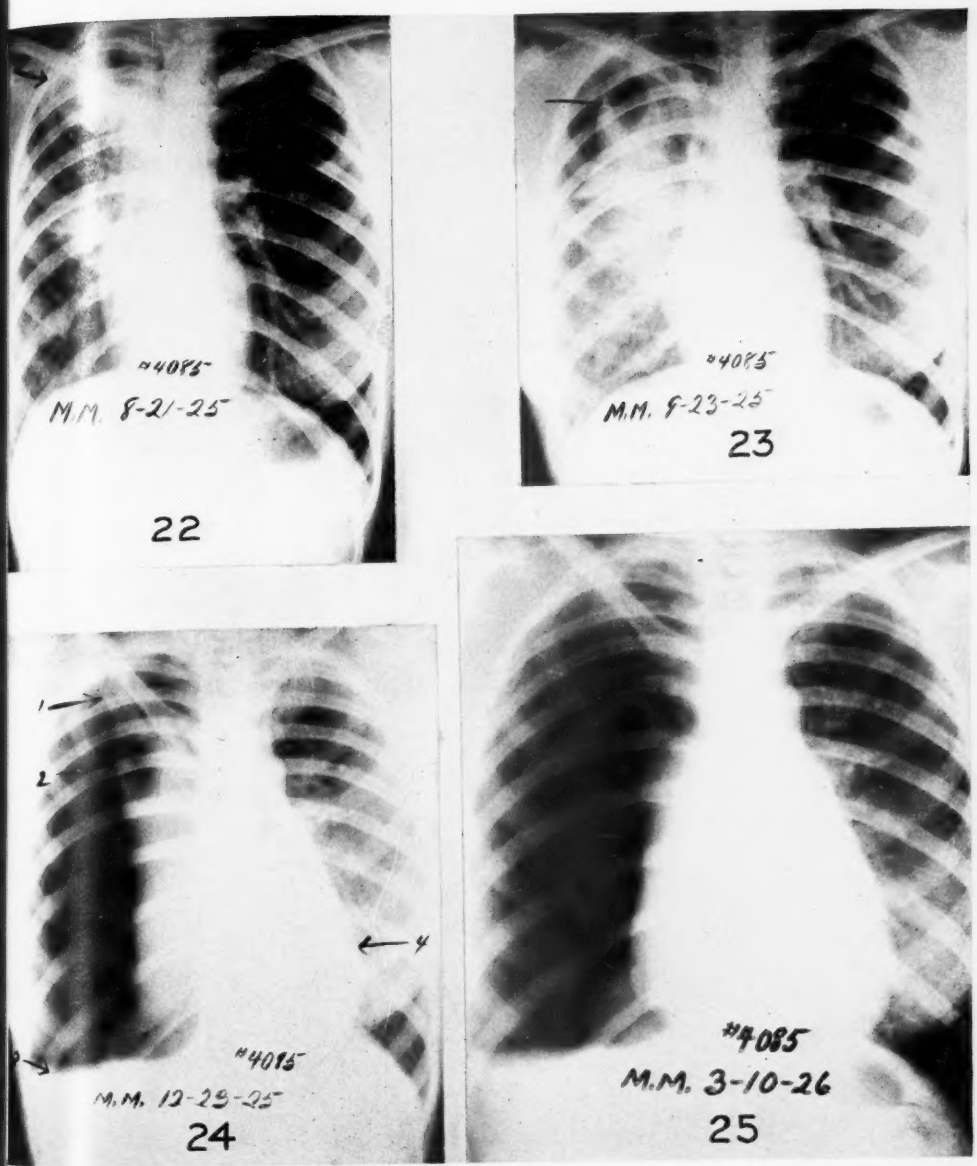

#4085
M.M. 8-21-25
22
#4085
M.M. 8-23-25
23
1
2
4
#4085
M.M. 12-29-25
24
#4085
M.M. 3-10-26
25

PLATE 12

PLATE 13

Fig. 26. Case 5157. Female; age 30 years; sick six months; sputum 20 cc. in 24 hours, tubercle bacilli positive; weight 120 pounds; temperature 101°F.

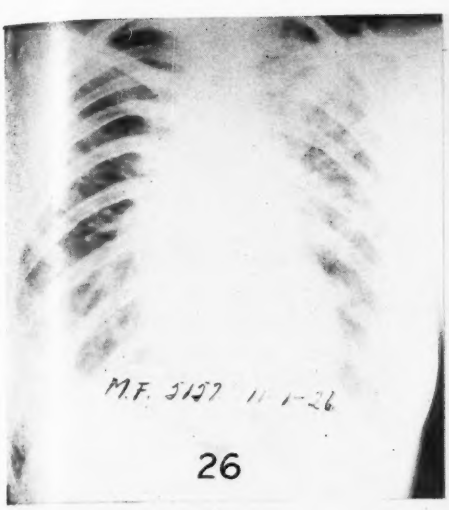
Fig. 27. Case 5157. Pneumothorax five months. Sputum 28 cc. in 24 hours, tubercle bacilli positive; weight 139 pounds; temperature normal

1: Adhesions preventing collapse of the lung

2, 3 and *4:* Displacement of diaphragm, mediastinum and heart. Cauterization indicated because of stationary quantity of sputum

Fig. 28. Case 5157. Seven days after cauterization. Sputum reduced to 5 cc. in 24 hours, tubercle bacilli positive; seven days later sputum denied

Fig. 29. Case 5157. Two months after cauterization. No sputum; temperature normal; weight 152½ pounds. One and one-half years later patient working, but still under pneumothorax and without sputum



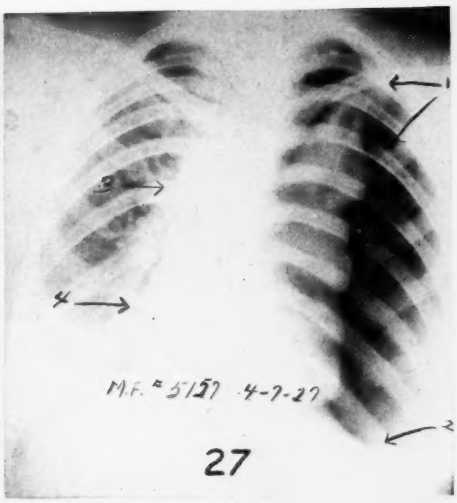


PLATE 13

PLATE 14

Fig. 30. Case 5246. Female; age 37 years; sick eight months; temperature 100° to 102°F.; loss of weight 15 pounds in spite of three months' bed-rest; sputum 26 cc. in 24 hours, tubercle bacilli positive

Fig. 31. Case 5246. Pneumothorax four months. Sputum reduced to 15 cc., tubercle bacilli positive; temperature 100°F.; constant loss of weight due to anorexia and pressure pneumonia; distressing cough followed gas refills

1 and *2:* String-adhesions preventing collapse of lung

3: Mediastinal displacement

Cauterization indicated because of uncomfortable pressure symptoms

Fig. 32. Case 5246. Four days after cauterization. Sputum denied; temperature normal in two weeks; gain in weight and disappearance of anorexia followed at once after cauterization. Nine months later patient still free from sputum

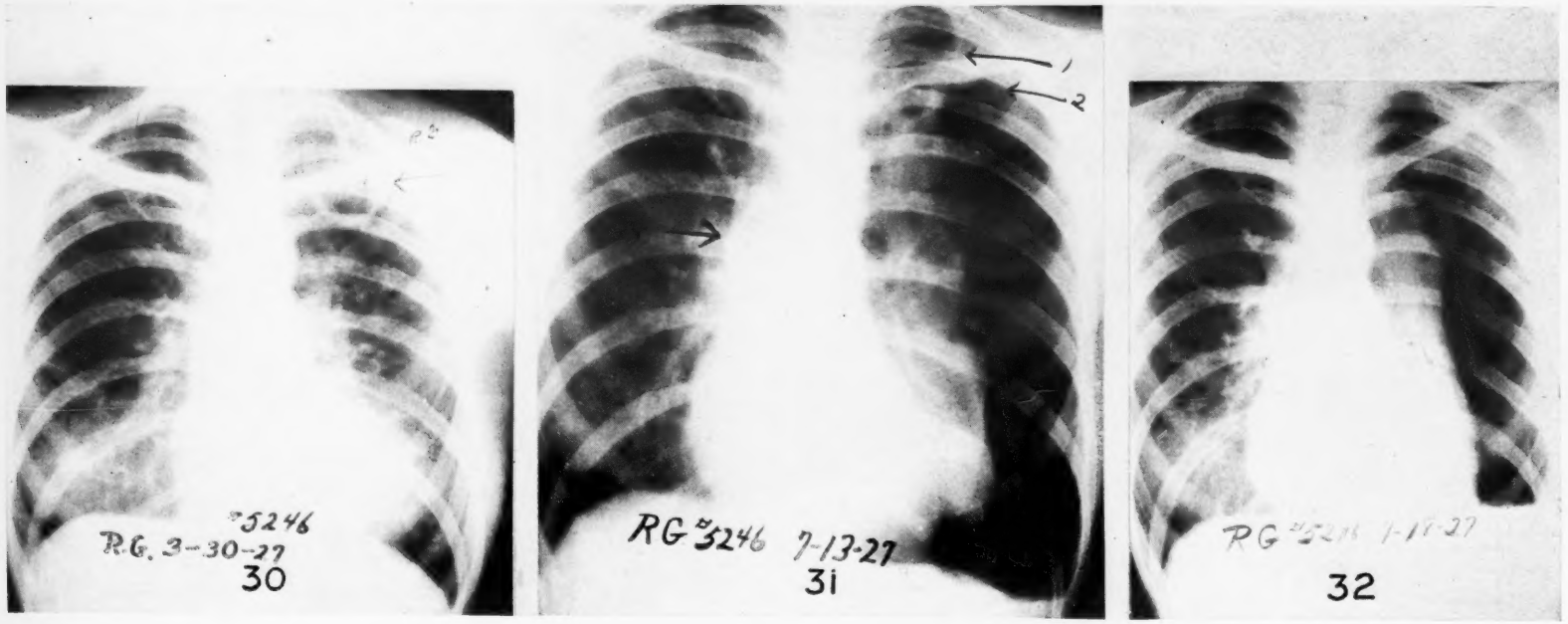


PLATE 14

PLATE 15

Fig. 33. Case 5308. Male; age 26 years; pneumothorax treatment four years. Tuberculous pyothorax last two years. Sputum became negative for tubercle bacilli after six months' pneumothorax treatment and remained negative one and one-half years; then became positive, with repeated haemoptysis, the past two years. Average 24-hour quantity of sputum, 15 cc.

1 and *2:* String-adhesions expanding the collapsed lung

3: Purulent exudate

Fig. 34. Case 5308. Two days after cauterization of adhesions and injection of 250 cc. 5 per cent oil of gomenol. Sputum 10 cc., tubercle bacilli positive

1 and *2:* Chest-wall stumps of adhesions

3: Oil of gomenol

Note improved collapse of lung

Fig. 35. Case 5308. Two and one-half months after cauterization. No sputum; no further haemoptysis. Complete collapse of lung. Oil of gomenol in pneumothorax space, 750 cc. One year later patient is working; no further haemoptysis; no sputum. Oleothorax being continued

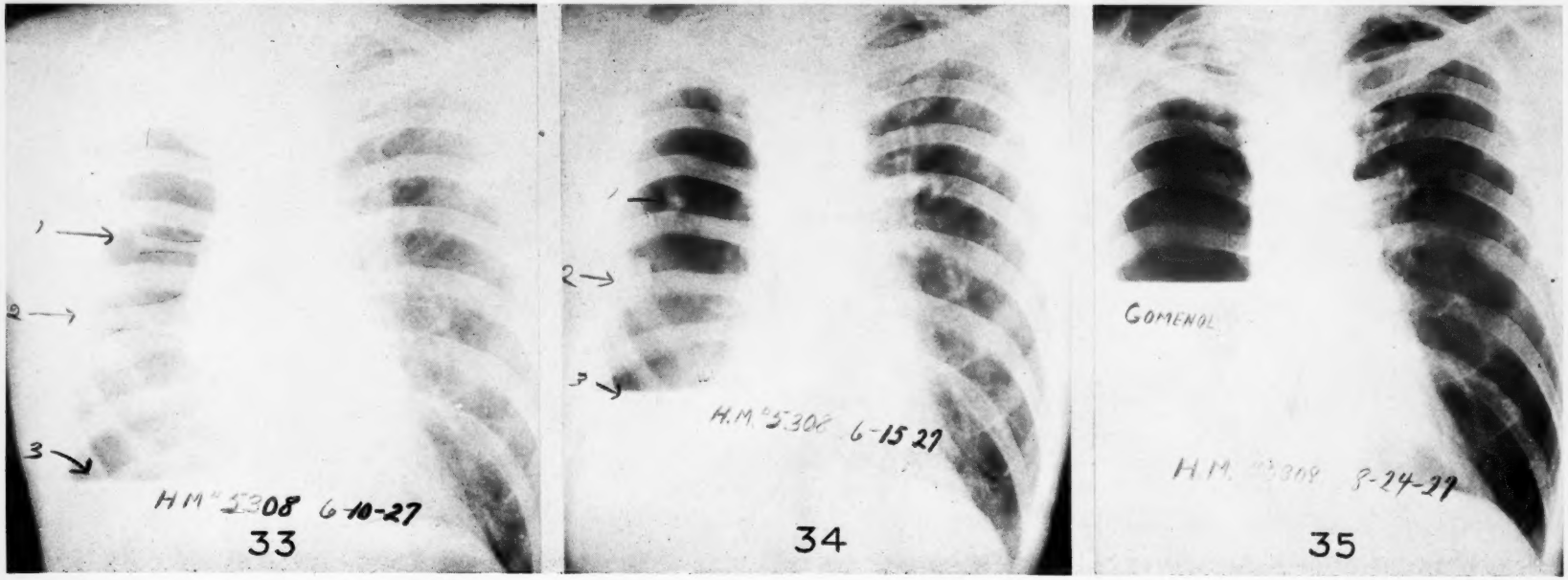


PLATE 15

PLATE 16

Fig. 36. Case referred for cauterization of band-adhesion at *1* supposedly holding open a cavity (*2*). Original films not available at the time. Thoracoscopic examination revealed *1* to be the floor of another uncollapsed cavity. Later study of the original film showed two large cavities in the upper lobe of the left lung

Fig. 37. Case 5202. Apparently a broad band-adhesion (*1*) preventing collapse of the lung. *2:* Slender band-adhesion at the base. Twenty-four-hour quantity of sputum, 50 cc., suggesting utilization of cauterization

Fig. 38. Case 5202. Original film of same patient shown in fig. 37. Average quantity of sputum for 24 hours, 80 cc. Comparison of the two films suggests that what appears to be a band-adhesion in fig. 37 is the floor of the cavity shown in fig. 38. Thoracoscopic examination confirmed this opinion

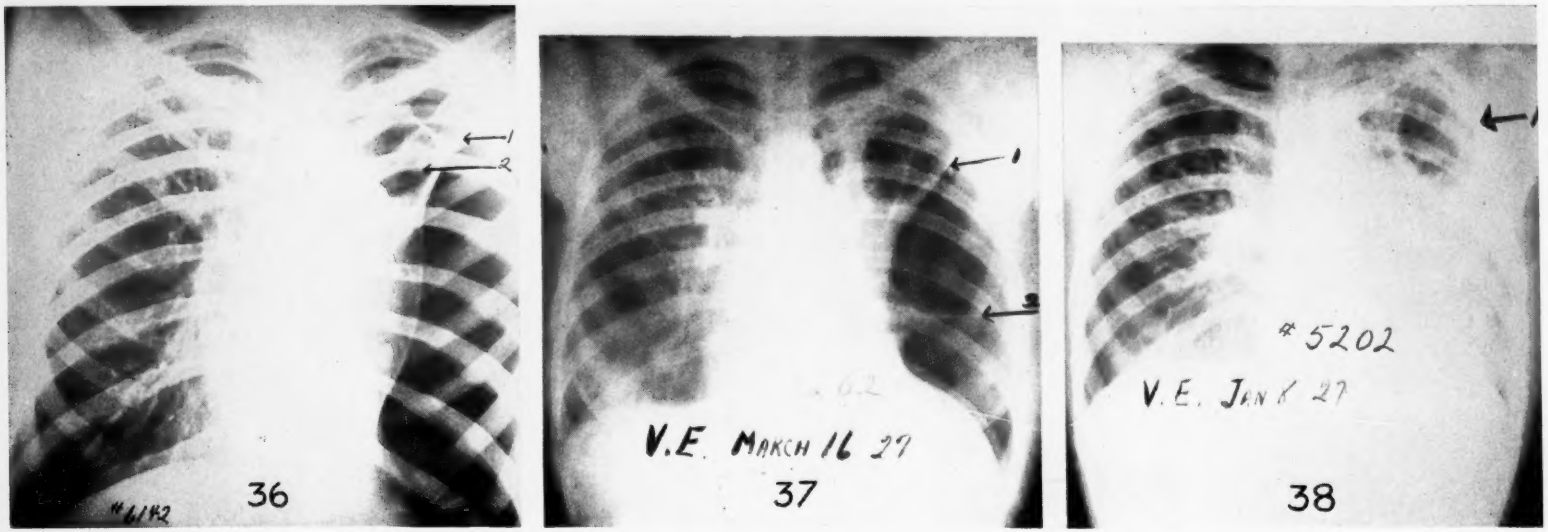


PLATE 16

PLATE 17

Fig. 39. Case referred for cauterization of a band-adhesion. The two fluid levels shown on the film were thought to be fluid in two pneumothorax compartments

1: Supposed upper compartment

2: Supposed band-adhesion

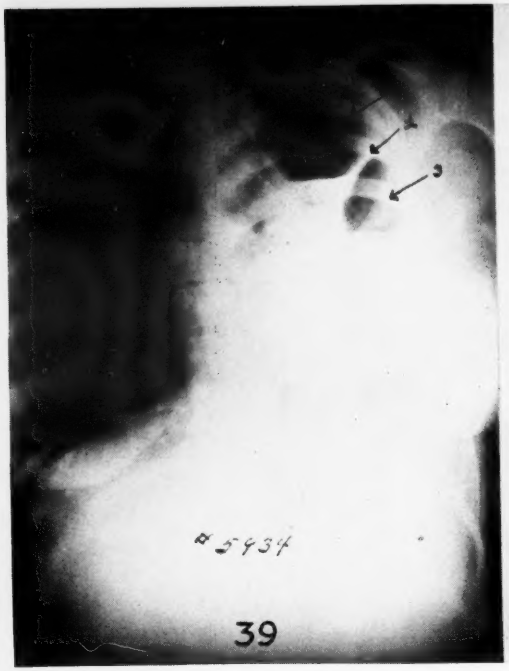
3: Supposed lower compartment

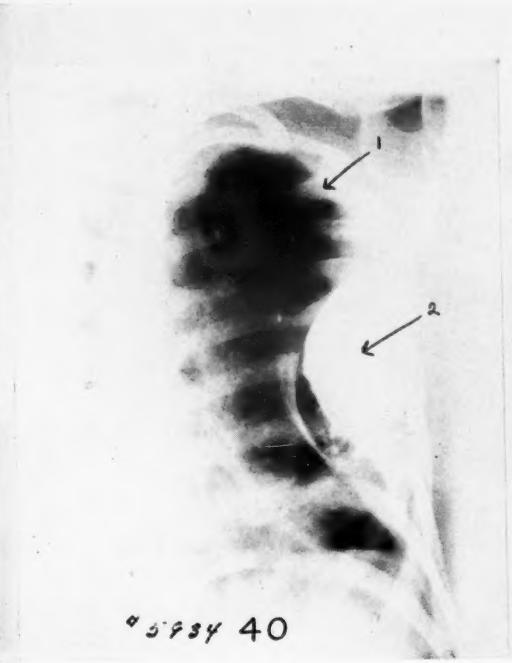
Fig. 40. Posterior view of same case, showing 20 cc. lipiodol injected into the pneumothorax cavity below, and the patient filmed with head down. The lipiodol remains confined in the lower compartment

1: Uncollapsed cavity

2: Lipiodol in pneumothorax

Fig. 41. Case 5334. Apparent band-adhesion (*1*) between a partially collapsed lung and lateral chest-wall. Referred as appropriate for cauterization. Thoracoscopic examination revealed a fold-adhesion, with thick anterior edge, extending around the posterior wall of the pneumothorax cavity to lateral wall. Numerous very slender string-adhesions were present at points indicated by arrows. *XX* indicates the attachment of the lung to the posterior wall of the pneumothorax. A thick fold-adhesion is shown at *2* and a thick band at *3*. Case unsuited for cauterization





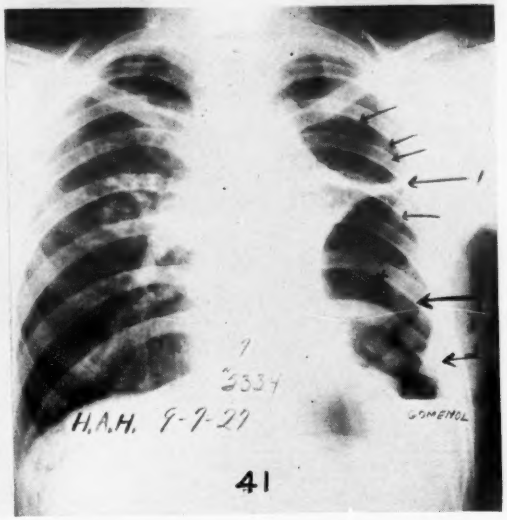


PLATE 17

PLATE 18

Fig. 42. Thoracoscopic view of a diffuse fold-adhesion

1: Diffuse fold-adhesion between lung and lateral chest-wall with thick anterior edge which appeared as a string- and band-adhesion on the X-ray film. Its dark gray color at *b* on thoracoscopic examination suggested either lung tissue or increased thickness of the adhesion

2: After cutting the free edge, an additional dense fold containing lung tissue (*b*) was found extending to the posterior wall of the pneumothorax space and not suited for cauterization. Cutting the free edge permitted the remaining portion of the adhesion to stretch, improving the collapse. A partial thoracoplasty was then done. The patient is clinically well

Fig. 42

PLATE 18

PLATE 19

Fig. 43. Case 6093. Female; sick one year; sputum 40 cc. in 24 hours, tubercle bacilli positive; afternoon temperature 100° to 101°F.

Fig. 44. Case 6093. Pneumothorax six weeks. Sputum 25 cc. in 24 hours; afternoon temperature average 100°F.

1, 2, 3 and *4:* String- and band-adhesions

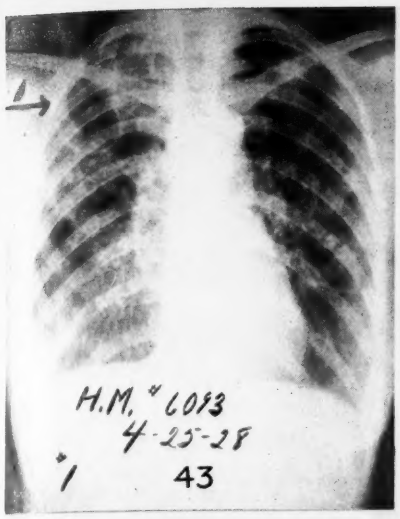
5 and *6:* Tuberculous cavities

Fig. 45. Case 6093. Pneumothorax two months and immediately after cutting adhesions posteriorly at *1* and *4*. Cavity *5* is smaller, but *6* uninfluenced. Average quantity of sputum in 24 hours, 20 to 25 cc.

Fig. 46. Case 6093. Pneumothorax nine weeks and immediately after second cutting of adhesions anteriorly. Small cavity shown at *5*, fig. 44, is collapsed but the large cavity has been uninfluenced

1 and *2:* Represents the shadow of what appeared as a fold of pleura extending from the lung across the posterior wall of the pneumothorax space

Fig. 47. Case 6093. Twenty cubic centimetres of lipiodol were injected into the pneumothorax cavity and its movements studied under the fluoroscope while the patient stood upright. The patient was then placed upon the fluoroscopic table and the head of the table slowly lowered to a horizontal position. The film was taken in the latter position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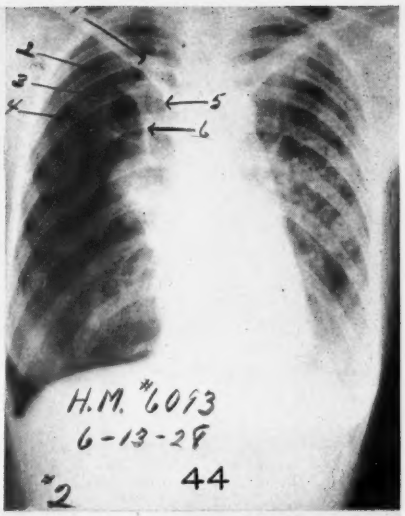
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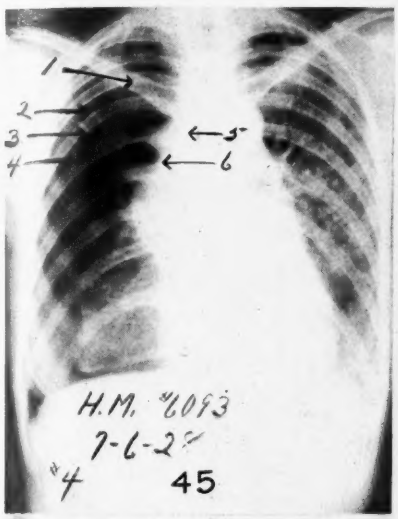
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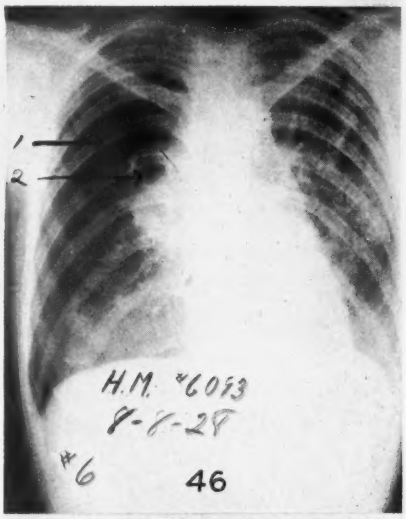
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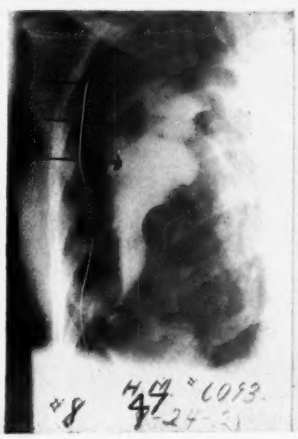
#8 47

PLATE 19

PLATE 20

Fig. 48. Case 6093. Thoracoscopic view of adhesion shown in fig. 46 (*1* and *2*)
a: Chest-wall attachment
b: Upper lobe of right lung
c: Lower lobe of the right lung
d: Intercostal muscle
e: Rib

Fig. 49. Case 6093. Thoracoscopic view of adhesion, showing use of author's blunt electrode for purposes of exploring nature of tissue before cutting. This instrument is also used for electrocoagulation of tissue, to obliterate large blood- and lymph-vessels before cutting

Fig. 50. Case 6093 Thoracoscopic view of adhesion shown in fig. 46 (*1* and *2*) after cutting with endothermic electrode
a: Lung stump
b: Chest-wall stump

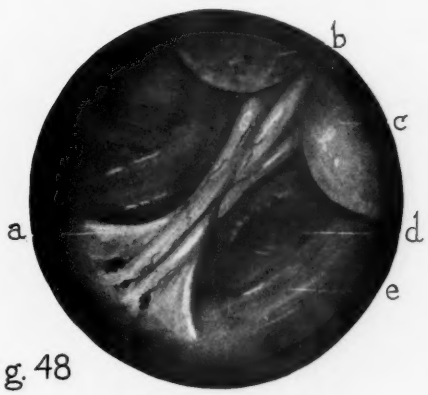

Fig. 48

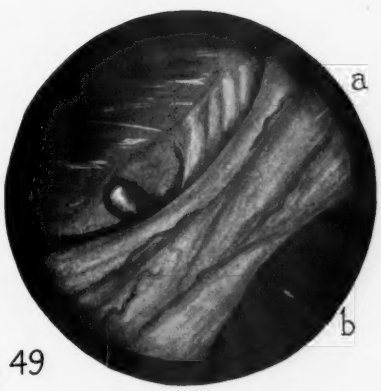

Fig. 49

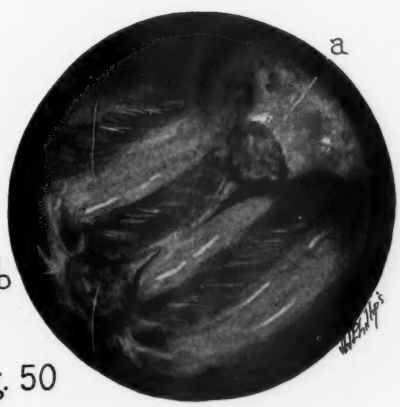

Fig. 50

PLATE 20

PLATE 21

Fig. 51. Case 6093. At once, after third cauterization, note improved collapse of cavity, *3*

1: Chest-wall stump of adhesion

2: Small fold of pleura of no technical importance, which extended from the adhesion shown in fig. 48 to the posterior chest-wall

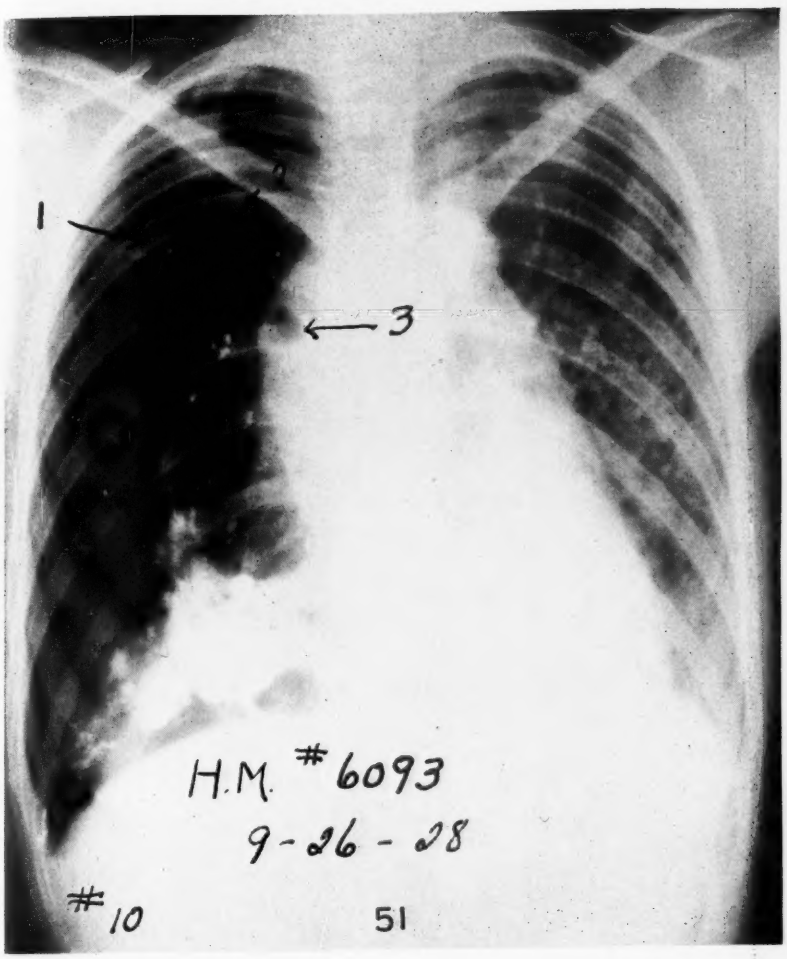

PLATE 21

PLATE 22

Fig. 52. Case 6172. Female; sick one and one-half years. Large tuberculous cavity in the upper lobe of the right lung (*1*) with bronchogenic dissemination to opposite side (*2*). Sputum 40 cc., positive for tubercle bacilli

Fig. 53. Case 6172. Pneumothorax five weeks. Cavity (*1*) collapsing away from chest-wall. No adhesions visible, but suspected because the pulmonary collapse and intrapleural pressure following subsequent inflations were not in proportion to the amount of air injected. Sputum 30 cc.

Fig. 54. Case 6172. Pneumothorax seven weeks after large refill of air. Stereoscopic films revealed apparent string-adhesions at *1* and *3*. Uncollapsed cavity (*2*). Quantity of sputum, 30 cc., only slightly influenced by pneumothorax

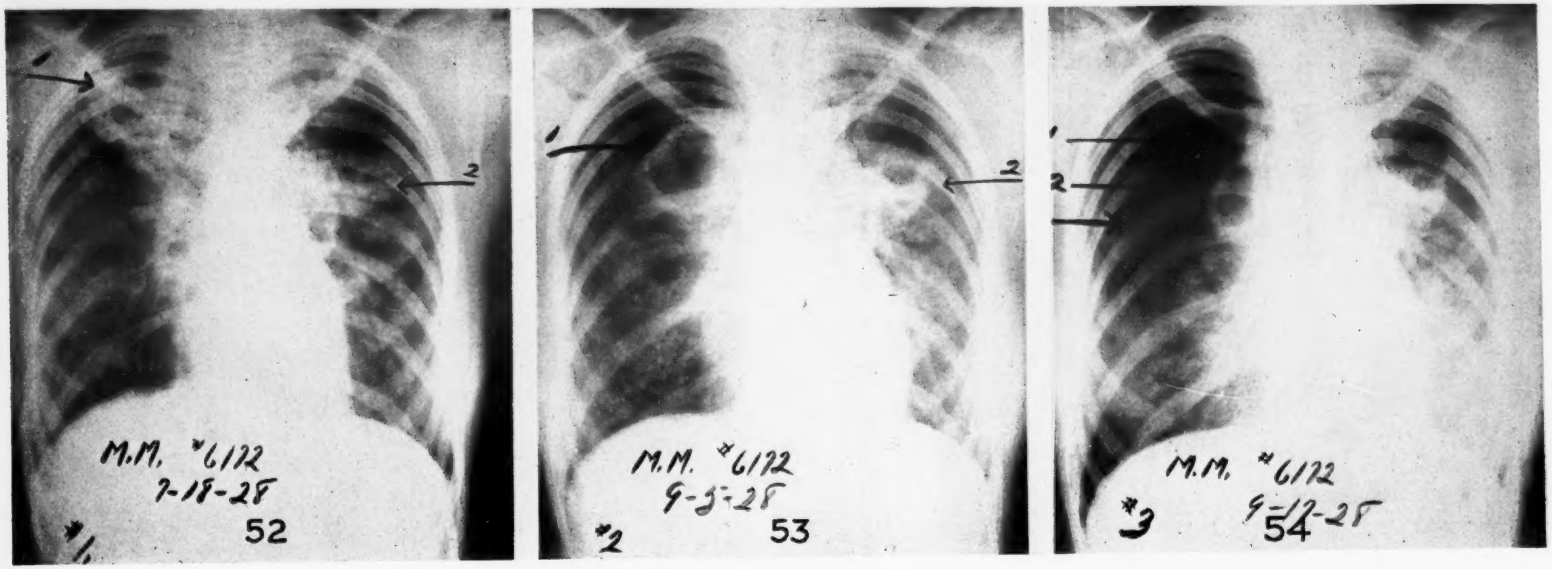

PLATE 22

PLATE 23

Fig. 55. Case 6172. Thoracoscopic view of a string-adhesion, 5 mm. wide, shown in fig. 54, extending from the upper lobe of the right lung near the interlobar fissure to the lateral chest-wall

a: String-adhesion

b: Middle lobe

c: Upper lobe

d: Caseous tubercles at the base of the adhesion

Fig. 56. Case 6172. Thoracoscopic view of apex of right lung

a: Fan-shaped adhesion extending from the apex to just above the sternal end of the first rib. This adhesion appeared as a mere string (*1*) on the film shown in fig. 54

b: The blue line near the border of the adhesion (*a*) suggested the presence of a blood-vessel

c: Superior vena cava, 2.5 cm. distant from the adhesion

d: Lung

e: Intercostal vein

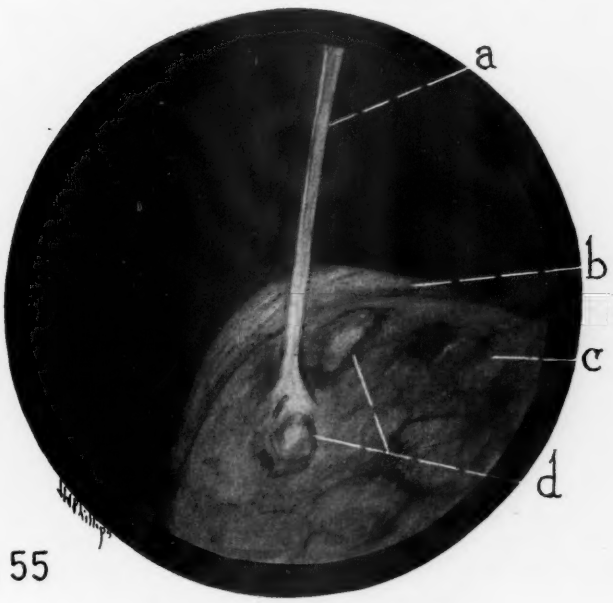

Fig. 55

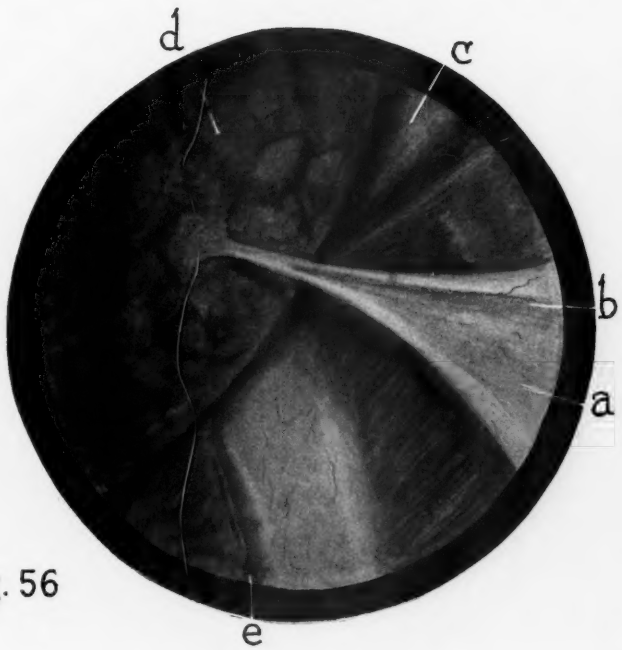

Fig. 56

PLATE 23

PLATE 24

Fig. 57. Case 6172. Method of examining structure of adhesion with author's blunt electrode *c*. The blue line, *b*, suggesting the presence of a blood-vessel, proved to be merely a very thin part of the adhesion as shown by its transparency

Fig. 58. Case 6172. Thoracoscopic view of adhesion cut by endothermy
a: Chest-wall stump
b: Lung stump
c: Lung

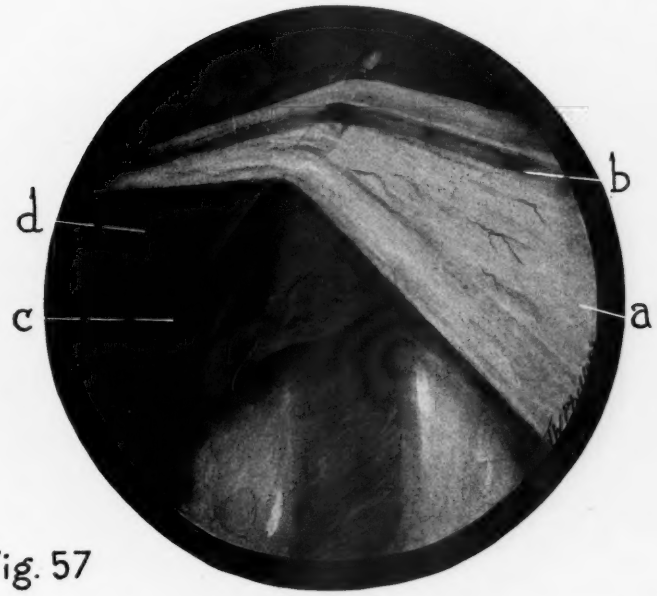

Fig. 57

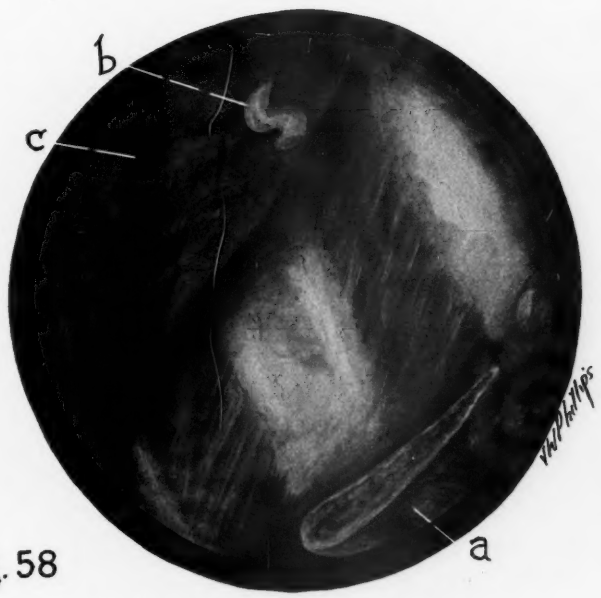

Fig. 58

PLATE 24

PLATE 25

Fig. 59. Case 6172. At once, after cutting adhesions shown in fig. 54. Note increased collapse of cavity (*I*). One week after cutting adhesions the sputum was reduced to 5 cc. in 24 hours

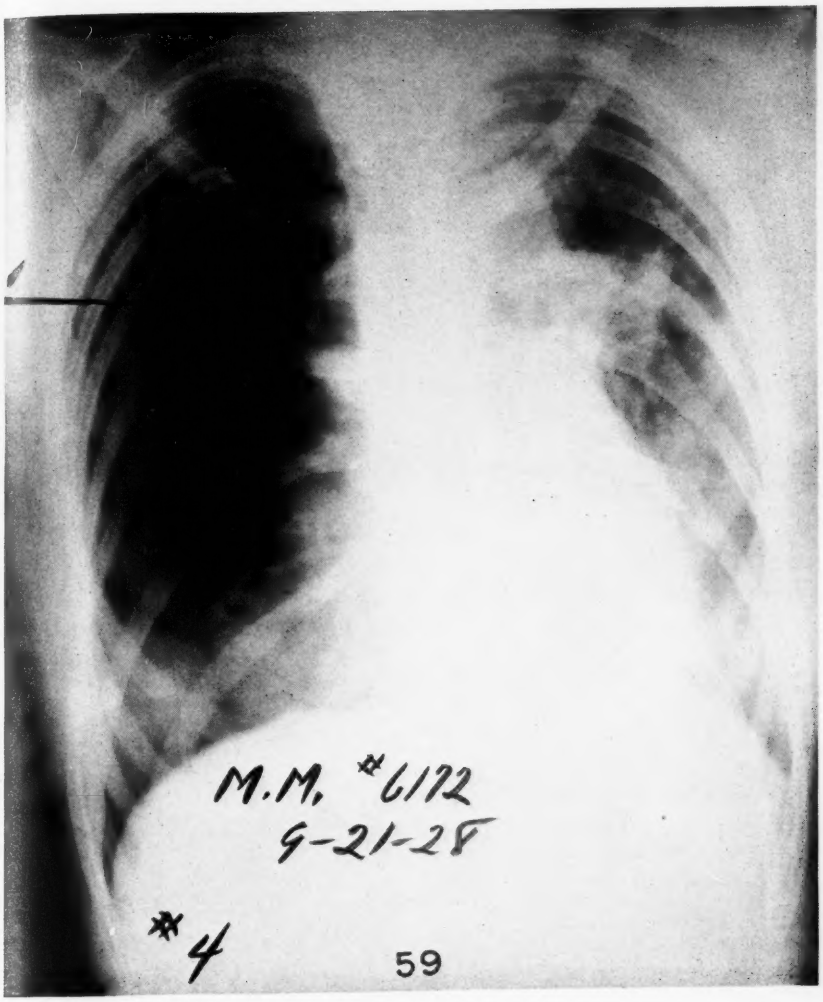

PLATE 25

PLATE 26

Fig. 60. Case 5306. Female, age 28 years; sick one year; sputum 160 cc., tubercle bacilli positive; temperature 100° to 101°F.; weight 116 pounds. Large cavity in apex with multiple cavitation in upper and lower lobes of left lung

Fig. 61. Case 5306. Pneumothorax two months. Sputum 60 cc., tubercle bacilli positive; temperature normal; weight 118 pounds. Uncollapsed large apical cavity, with three smaller uncollapsed cavities. Multiple string- and band-adhesions at *1*, *2*, *3*, *4* and *5*

Fig. 62. Case 5306. Six days after cauterization of adhesions at *2*, *3*, *4* and *5*. Apical adhesion not cauterized because of presence of lung tissue close to chest-wall. Sputum reduced to 25 cc. Temperature normal. Ten days later sputum was reduced to 10 cc. daily

Fig. 63. Case 5306. Four months after cauterization. Sputum still absent nine months after operation. Remaining apical adhesion not interfering with collapse of lung

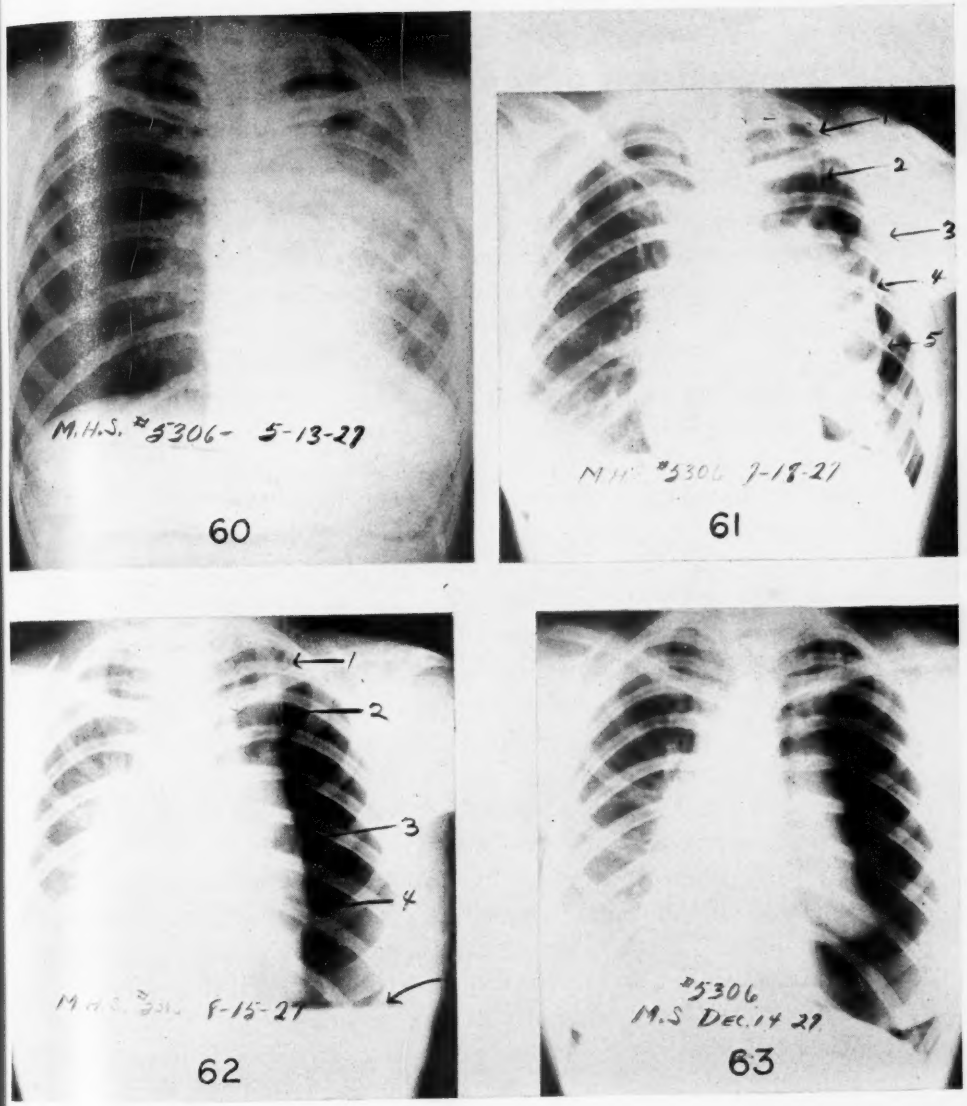

PLATE 26

A SIMPLIFIED OPERATING THORACOSCOPE[1]

LOUIS R. DAVIDSON

Surgical intervention in the treatment of either advanced or progressive tuberculosis has, as authorities concede, a definite and logical place in the treatment of the disease. Any procedure which compels the lung to fall in toward the mediastinum may be included under the term "Collapse Therapy." Depending upon the method employed,—artificial pneumothorax, thoracoscopy with cauterization, phrenicotomy, extrapleural thoracoplasty, extrapleural pneumolysis and apicolysis,—the lung is left completely or partially in a temporary or permanent condition of compression. Although these different methods of collapse therapy are based upon the same fundamental principles, yet the individual case (more specifically the state of the pleura) determines the procedure employed. Instruments suitable for phrenicotomy, extrapleural thoracoplasty, apicolysis and extrapleural pneumolysis, are found in the operating room of average equipment; whereas the laboratory furnishes parts which can be readily fashioned into a serviceable artificial-pneumothorax outfit. However, when internal pneumolysis (for the purpose of this article,—thoracoscopy and coagulation) is resorted to, one must possess a specially constructed instrument.

I have used and, for quite some time, have witnessed others employ the thoracoscope devised by Jacobaeus (1) and modified by Unverricht (2). This instrument, although ingenious in its origin and at times, when used in suitable cases (3), astounding in its effectiveness, is managed with the utmost difficulty, and is withal more complex in structure than one would expect. This fact has stimulated others (4) (5) to modify both the apparatus and, concomitantly, the technique.

This article describes an instrument[2] which, I believe, is less complicated in structure, more consistently surgical, and less difficult of manipulation than any heretofore devised. The optical system[3] is an extreme

[1] From the Department of Surgery, Service of Dr. Charles Gordon Heyd, Post Graduate Hospital, New York City.

[2] The operating thoracoscope is manufactured by the American Cystoscope Makers, Inc.

[3] In this instrument McCarthy's Foroblique Lens System is utilized.

departure from that previously used; the means adopted for severing the adhesions is unique in that a high-frequency current coagulates and cuts them; while, finally, but one thoracic-puncture wound is necessary to permit of observing the pathological changes and dividing the bands.

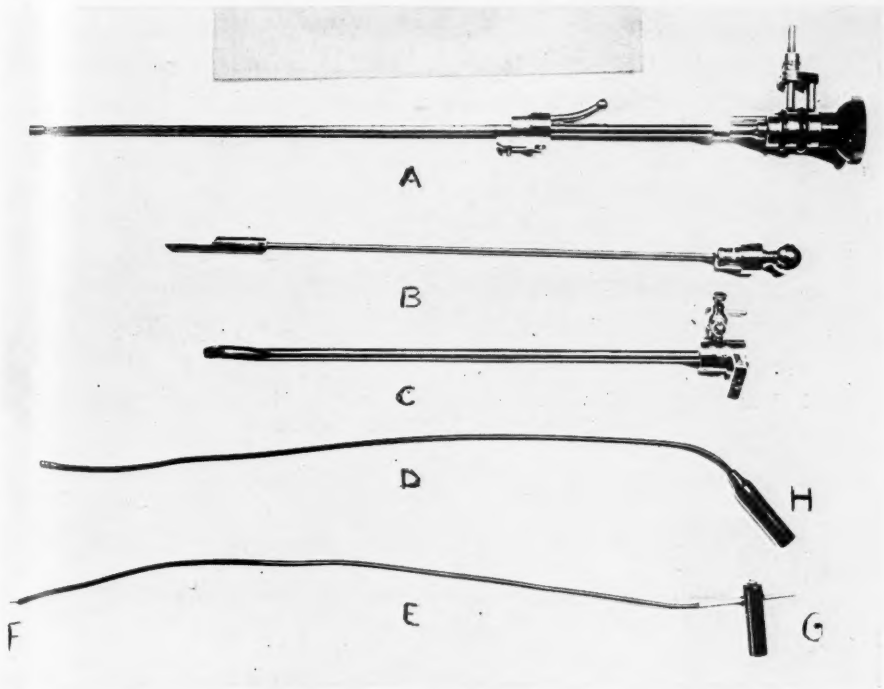

FIG. 1. AUTHOR'S OPERATING THORACOSCOPE

A: Thoracoscope containing lamp, McCarthy's foroblique lens system, and channel for passage of electrode
B: Trocar
C: Cannula with beaked extremity and outlet which connects with air-pressure apparatus
D: Coagulating electrode
E: Cutting electrode

The parts of the instrument are illustrated in figure 1 and consist of the following:

A: Thoracoscope containing lamp and McCarthy's "foroblique" lens system and channel for passage of electrode
B: Trocar
C: Cannula with beaked extremity and outlet which connects with air-pressure apparatus

D: Coagulating electrode
E: Cutting electrode

Figure 2 illustrates the trocar and cannula assembled prior to their introduction through an intercostal space, while figure 3 illustrates the thoracoscope substituted for the trocar and the electrode in place.

After the trocar and cannula have been introduced into the pleural cavity through an intercostal space, the site of which has been previously determined by proper radiographic and fluoroscopic exposures, the thoracoscope is substituted for the trocar. Through the optical system the

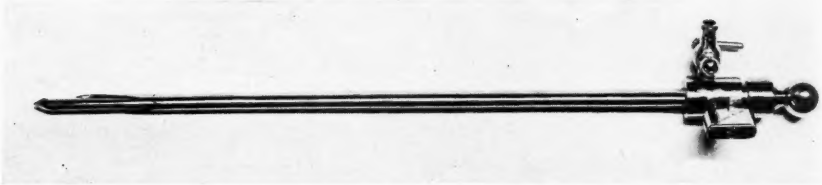

FIG. 2. ILLUSTRATES THE TROCAR AND CANNULA ASSEMBLED PRIOR TO THEIR INTRODUCTION THROUGH AN INTERCOSTAL SPACE

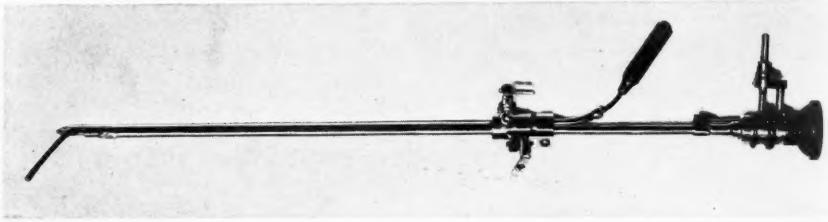

FIG. 3. ILLUSTRATES THE THORACOSCOPE SUBSTITUTED FOR THE TROCAR AND THE ELECTRODE IN PLACE

type of adhesions and the condition of the pleura are observed; if the pathological conditions noted warrant operation, then the coagulating electrode is inserted. With its bulbous terminal upon the adhesion band and the inactive rolled-tin electrode upon the chest-wall, the foot-switch is depressed, thereby permitting the current to flow. When the adhesion has been sufficiently treated (coagulated) the cutting electrode replaces the one already used. Now a cutting current is sent through the electrode, whose twisted wire end is placed upon the band at the centre of the part previously coagulated. Various factors, such as body-resistance, fluid-flow, etc., will determine the rapidity with which the adhesion is severed. Thus the lung, which heretofore could be only

partially collapsed by means of artificial pneumothorax, is now in a condition to be completely collapsed by an additional refill because the fixating or limiting membranes have been divided.

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(2) Unverricht: Weitere Erfahrungen mit der Kaustik im Pleuraraum und der Thorako- und Laparoskopie, Ibid., 1923, lv, 296.

(3) Jacobaeus, H. C.: The cauterization of adhesions in artificial pneumothorax treatment of pulmonary tuberculosis. Technique and indications, together with a survey of results obtained thus far, Amer. Rev. Tuberc., 1922, vi, 871.

(4) Singer, J. J.: The thoracoscope in pulmonary diagnosis, Ibid., 1924, x, 67.

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HAEMOPTYSIS IN TUBERCULOSIS FOLLOWED BY MASSIVE PULMONARY ATELECTASIS

A Case Report[1]

JULIUS L. WILSON

Haemoptysis, complicated by pulmonary atelectasis, is extremely rare. The atelectasis may be logically attributed to the occlusion of a bronchus by a blood-clot, but in no instance apparently has this point been verified by the recovery of the clot. The case here reported is of interest because the patient expectorated a bronchial cast composed of a blood clot, and with its expectoration, the pulmonary atelectasis rapidly disappeared.

Mrs. S., aged 23, entered the New York State Hospital on September 18, 1927, with a history of an attack of influenza of brief duration in February, 1926, followed by a dry hacking cough and malaise. She had an haemoptysi[illegible] few ounces two months later, but the nature of her disease, tuberculosi[illegible] is not recognized until a subsequent small haemoptysis in August, 1927.

The patient, of medium build and in very fair nutrition, had no outspoken symptoms, except a slight productive cough. Tubercle bacilli were pr[illegible] in the sputum. There were slight dulness, altered breath-sounds, and l[illegible] râles over the upper third of the right chest; otherwise physical examina[illegible] was negative. The chest roentgenograph confirmed the location and ext[illegible]nt of the pulmonary lesion, and further revealed the presence of a small ar[illegible] in the second interspace (figure 1).

The condition of the patient was excellent for the first three weeks, w[illegible] temperature, pulse and respiration were normal. But on October 10th, [illegible]ith no premonitory symptoms, the patient spat 16 oz. of blood, and during the next two days expectorated only half an ounce of blood, mostly clotted. Her maximum temperature was 100.6°, pulse 110, and respirations 20; she w[illegible] calm and coöperative.

Three days after the onset of the haemoptysis, on the evening of October 1[illegible] the patient quite suddenly began to complain of difficulty in breathing. [illegible] was in evident distress and slightly cyanotic. Her respiratory rate [illegible] to 40, and a few hours later to 50; her temperature was 101.4°, and

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

pulse 136. The physical signs were in striking contrast to those of a few weeks previously. The right side of the chest was markedly shrunken and immobile except for a slight movement at the summit, while the respiratory movements were exaggerated on the opposite side. Pulsations were visible for a distance of 4 cm. beyond the right sternal border from the second to the fifth intercostal space, and the apex-beat of the heart was palpable at the left sternal border in the fifth intercostal space. The trachea was displaced to the right, lying behind the head of the right clavicle. Vocal fremitus was

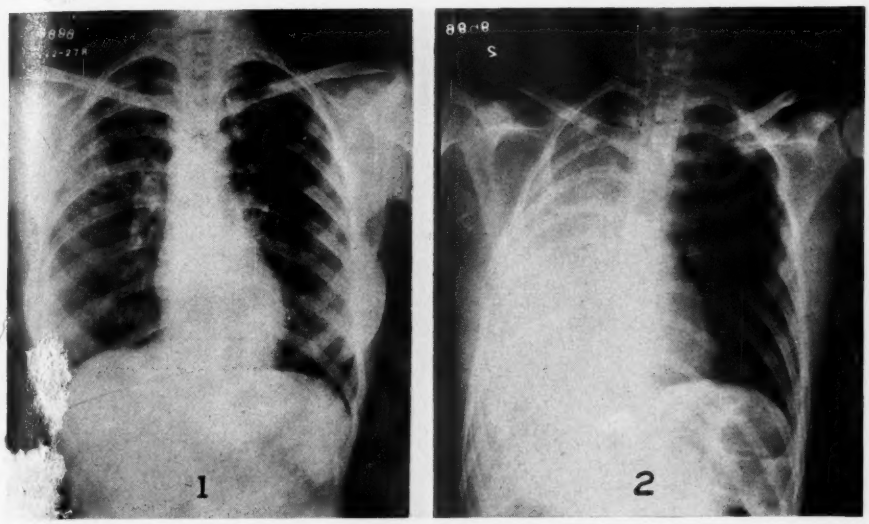

FIG. 1. ROENTGENOGRAPH SEPTEMBER 22, 1927

Tuberculous infiltration of right upper lobe; clear circle in second interspace

2. BEDSIDE EXPOSURE OCTOBER 16, 1927, THREE DAYS AFTER ONSET OF DYSPNOEA

Mediastinum shifted to right; lower two-thirds of right lung opaque; narrow shadow over apex

increased over the entire right chest. There was dulness on percussion anteriorly from the apex to the third rib, with a tympanitic quality in the third interpace, and below this point flatness. Posteriorly, the note was dull to the ...h dorsal spine, and flat below. The lower border of liver dulness in the mid-...vicular line was 3 cm. above the costal margin. The breath-sounds were ...nchial from the apex to the second rib, and absent below. The left lung, except for hyperresonance and exaggerated breath-sounds, presented no abnormal signs. The above physical signs revealed that there had been a sudden and marked decrease in the volume of the right lung, evidence sufficient

to warrant the diagnosis of massive pulmonary atelectasis. The patient was kept very quiet because of her critical condition and also the danger of aspiration of the infected blood-clot that was presumably obstructing the bronchus. However, three days after the onset of the urgent dyspnoea, on October 16th, the symptoms had somewhat abated, and the physical signs indicated that the upper portion of the right lung had become more fully aerated. A chest roentgenograph was taken at the bedside with a minimum of disturbance to the patient (figure 2). The right lung-field now showed a uniform dense

FIG. 3. BRONCHIAL CASTS, ACTUAL SIZE, OF CLOTTED BLOOD AND FIBRIN EXPECTORATED IN AFTERNOON OF OCTOBER 19, 1927

shadow from the base to the second rib and shadows less dense and uniform above. There was also a faint uniform shadow arching over the apex and extending peripherally down to the second rib. The trachea and mediastinum were displaced to the right. The left lung-field was normal. This roentgenograph confirmed the physical findings in all essentials and, in addition, suggested the presence of a small pleural effusion.

On the following day, October 17th, on the evidence presented by the roentgenograph, thoracentesis was performed low in the midaxillary line. It was possible to recover only 50 cc. of clear straw-colored fluid, after which 100 cc.

of air were introduced into the pleural cavity. With the patient in the supine position the intrapleural pressure readings were then −12 cm. water on inspiration and −10 on expiration. The introduction of air into the pleural cavity permitted one to locate, by the aid of the fluoroscope, the position of the right leaf of the diaphragm, which was high and immobile.

On this day and the next (October 17th and 18th) the patient expectorated small amounts of clotted blood. On the following day (October 19th) she expectorated about 2 oz. of clotted blood, in which were found three bronchial casts, the largest 3 in. long with seven distinct branches (figure 3).

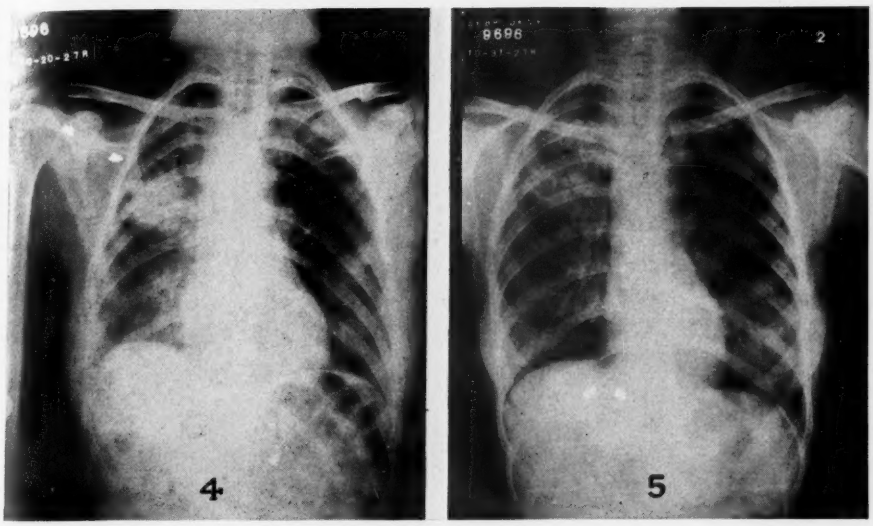

FIG. 4. BEDSIDE EXPOSURE (PATIENT SUPINE) ON OCTOBER 20, 1927

Mediastinum returned to midline; aeration of lower half of right lung; small residual pneumothorax at right apex

FIG. 5. TWELVE DAYS AFTER EXPECTORATION OF CASTS

Complete restoration of *status quo* before haemoptysis

Haemoptysis ceased at this time, and the patient's condition rapidly improved. The temperature, pulse and respiration returned to normal almost immediately. The next morning, October 20th, a roentgenograph was taken, showing that the lung had practically returned to its normal volume, as shown by the size of the right lung-field, the normal position of the mediastinum and the trachea (figure 4). Moist râles persisted over the right lower and middle lobes for one week and then disappeared. The patient continued to make excellent improvement, and was discharged from the Sanatorium eight months later with her pulmonary condition thoroughly arrested.

THE MIND AND TUBERCULOSIS[1]

BEN WOLEPOR

Contrary viewpoints are held by different writers on the influence of tuberculosis on the mind. One school of thought claims that pulmonary tuberculosis has a specific influence on the individual, producing a definite pattern of thought and conduct; the other asserts that phthisis differs slightly, if at all, from any other chronic disease in its effects upon the mind. The purpose of this paper was to determine which of the two views held approximates most closely the evidence gathered in the Wm. H. Maybury Sanatorium.

Jelliffe and White state (1) that the "shut-in" type of personality, which manifests itself in a tendency to withdraw from the social environment and lead a cloistered existence, may tend at the psychological level in the direction of dementia praecox and in the physiological level in the direction of pulmonary tuberculosis.

Leo Wolfer (2) went to the extent of calling dementia praecox the result of pulmonary tuberculosis. He compared tuberculosis to syphilis in that both, he claimed, produced psychoses; one dementia praecox, the other paresis. Although the hereditary relationship between dementia praecox and tuberculosis has been stressed, Jelliffe and White, however, think that studies on heredity are not as yet able to define what is inherited.

Clouston (3) said that the death-rate among insane patients from tuberculosis was three times as high as that in the general population. Hygienic conditions do not relieve the situation, he claims. His views are at variance with those of Huber, however, who says that the mentally ill permitted to go out of doors are not particularly prone to pulmonary tuberculosis. Laennec (4) stressed the influence of confinement within doors as a cause of the increased deaths amongst nuns who keep to the cloister, in comparison with those whose work leads them outside the convent walls.

Osnato (5) studied personality in paresis. He claims that the per-

[1] From the Wm. H. Maybury Sanatorium (Detroit Municipal Tuberculosis Sanatorium), Northville, Michigan.

sonality is merely influenced by the disease. Disease in itself does not produce a new personality. The distinctly psychotic forms of general paralysis develop in people with peculiar personalities. Jelliffe (6) claims that psychoses supposedly due to alcohol are dependent upon some peculiarity of make-up in the individual; alcoholism, he insists, is only a surface indication and the true aetiological factors lie deeper. Each man reacts to alcohol in a way peculiar to himself.

Laegnel-Lavastine (7) maintains that the mental state of the sick is merely an exaggeration of their psychic life during health; the lazy become indifferent, the active agitated. H. Carncross (8) insists that the question is not whether tuberculosis patients are particularly hopeful, optimistic or anything else, but do they undergo a change of mental state? This, he thinks, does occur to a limited extent, but he attributes the mental alteration to chronic disease rather than to tuberculosis alone. Engel (9) believes that the inherent mental characteristics become accentuated in the chronic tuberculosis patient. There is, he claims, an oscillation in the patient's attitude toward life which varies with the alterations in his health; the unexpected exacerbations and improvements influence his mental make-up. The inhibitions demanded by civilization are often disposed of by the diseased individual, and the man shines in his true light.

Fishberg (10) thinks that the optimism of the tuberculosis patient is evident from the onset of the disease. Only a profuse haemorrhage will frighten the average patient, who fully expects a speedy recovery. He adds that with the progress of the disease, his vivid illusions of a quick cure are beginning to disappear; he fears death, and his innate mental traits reveal themselves in an accentuated form, especially the bad ones. He becomes dissatisfied, irritable and emotionally unstable; quickly changing from hilarity to depression. Some patients become actual recluses, avoiding friends, despising sympathy, and growing despondent. These cases, he says, are rare, and Fishberg adds that few tuberculous patients commit suicide.

DeSantos Saxe (11) believes that tuberculosis plays the rôle that any other chronic disease would upon the psychical characteristics of the patient. It does not differ in this respect from heart-disease, he maintains. The latent characteristics, that a healthy self-control subjugated, arise now to their full dimensions, and the mental make-up of the individual is exposed. He, too, thinks that the gradual loss of self-control and will-power unmask the tuberculosis patient. He adds that this

loss of self-control is modified by the natural temperament of the individual, and the gravity of the disease; but he nevertheless maintains that loss of self-control, and selfishness play the most important parts in the moulding of the mental traits of the tuberculous.

Daremberg (12) said that the central nervous symptoms of tuberculosis patients were in evidence many years before the appearance of the ordinary signs of the disease. Whenever one regards in an adult a change of character, he maintains, especially a general carelessness and a marked incapacity to work, without a known cause, it is necessary to suspect the possibility of serious tuberculosis in the future. Head (13) says that tuberculosis gives neurasthenic symptoms. Richard Morton, quoted by Huber (14), observed that many tuberculosis patients display symptoms of neurasthenia. Papillon (15) suspects every victim of neurasthenia to be a subject of latent tuberculosis. Weir Mitchell's (16) good work in the treatment of neurasthenia depended largely upon the favorable results rest gave to unsuspected tuberculosis. DeSantos Saxe claimed that the early stages of tuberculosis are frequently accompanied by symptoms of neurasthenia.

Munro (17) admits that there is no such thing as a specific psychopathology of tuberculosis, and for such abnormal psychical reactions as may be noted we must seek, he claims, an explanation in the temperamental peculiarities of the individual. On the other hand, he asserts, other writers consider that there is a definite psychical state which may be fairly referred to as specifically characteristic of tuberculosis. He, like Cornet (18), considers the toxins of tuberculosis responsible for the psychoses produced. He adds that some authorities think that the mental and moral changes which have been noted are merely individual traits of temperament and conduct, which exist quite apart from the disease and are at most intensified in the course of a chronic and debilitating illness.

Munro further discusses the psychoneuroses of what he terms the middle stage of tuberculosis; although he adds that many patients show no deviation from the normal throughout their disease. He divides them into the asthenic, that is, the apathetic; the procrastinating type, possessing weakened will, attention and concentration,—they are irritable and susceptible to trifling annoyances; and the erethic, the patient who has more resistance to the disease, who is normally impulsive and excitable, and in whom there is an exaggeration of these characteristics as a result of the disease. They are not amenable to discipline. Their

intellectual and imaginative faculties are heightened at this stage of the disease. Genius flowers. One may detect the genesis at this stage of the suspicious attitude which becomes so prominent a feature in certain more advanced cases.

Munro describes the psychoneurosis of advanced tuberculosis, claiming that, although in the earlier stages of the disease it is impossible to refer to a specific type of psychopathology, when we come to the later phases of tuberculosis there are certain definite mental and moral reactions associated in a special sense with the disease. There is a diminution of the restless energy so noticeable in earlier states; periods of fatigue are more frequent and any intellectual effort is avoided. One of the most striking psychical changes is the curious apathy to the gravity of his condition so often displayed by the patient.

Less frequently, Munro continues, we meet with patients who appear to be habitually analyzing their symptoms. Another type of patient is philosophical, and adapts himself to life's altered values. The patient may display at times the most contradictory mental states. Munro quotes Béraud to the effect that the patient is hypersensitive to himself, yet hyposensitive for others, but he qualifies this statement by adding that this is not true for the majority, who face the end with calmness and courage. He says that the optimism of the phthisical patient is to be regarded in a number of cases as an individual trait rather than a symptom of the disease. He modifies this statement by the qualification that it is, however, very often met with in the various stages of the disease and most characteristically in the advanced type of case. He attributes the terminal euphoria to profound toxaemia.

To show that neurasthenic symptoms are not peculiar to tuberculosis alone, Head says that many cases of latent syphilis give neurasthenic symptoms; so does nephritis, as well as gastric ulcer.

Kraepelin (19) speaks of a syphilitic neurasthenia appearing shortly after infection and manifesting itself by a nervous discomfort, difficulty in thinking, irritability, disturbance of sleep, pressure on the head, variable and changeable discomfort and pain. He also insisted that each acute infectious disease could in the course of further study be recognized by the mental symptoms alone. This viewpoint was combated by the French school. Pellagra, according to Menninger (20), is the only exception and a doubtful one at that.

Elliot (21), in discussing essential hypertension, says that the earliest evidence of progressive cardiac deficiency is nearly always subjective in

character. The patient complains of a certain decline in perception; feels fatigued after a night's rest; loses his emotional stability.

Jelliffe and White admit that many cases of neurasthenia are, it is true, due to obvious aetiological factors, such as tuberculosis, syphilis, arteriosclerosis; but in numerous cases an inability of the individual to get beyond the evolutional stage, where pleasure is sought in self, often causes neurasthenia.

The tuberculosis patient has been described by famous novelists and dramatists, and has even expired in *La Bohême*, to the strains of good music. Physicians have described the influence of tuberculosis on genius, and some regard it a favorable one in so far as the productivity of classics is concerned,—that it is an affliction which spurs into activity qualities which would otherwise have remained dormant if they had existed at all.

Tuberculosis is so prevalent that even the exalted minority of genius suffers at its hands. A superficial impression tempts one to say, "*post hoc, ergo propter hoc,*" but this is not so. Syphilis will occur in the great with the same consummate ease that tuberculosis infects them. Disease is no respecter of intellect. Swift and DeMaupassant were famous despite syphilis. All that this disease did was to hasten them precipitously to the mad-house and abruptly terminate their careers. Syphilis, as is well known, may also produce neurasthenic symptoms, a power which arteriosclerosis and tuberculosis possess, but none of these diseases possesses the magic alchemy whereby the dross in man is converted into gold; they cannot change mediocrity into genius.

Emil Ludwig, in his critical analyses of great men, differentiates them into two classes; those who, like some tropical fruit, come to a speedy ripeness; do their best work in a comparatively short period and cease, the Tschaikowsky type; the others, like Conrad, develop their powers by a laborious struggle. He notes the different tendencies of the two, and, although a layman, attributes them to inherent factors which the world only influences but does not transform.

To determine what influence pulmonary tuberculosis had upon the personality of the individual, a study of 100 patients was made. A mental history was obtained from each one; stress was laid upon his reaction to life before he contracted tuberculosis. Was he social or seclusive, introspective or shallow; how did he react to difficulties? Did he face or disregard them; brood or resign himself; gain ascendancy over life's handicaps, maintaining his poise; or did he remain uncertain in his

attitude? What were his relationships with his friends before tuberculosis came into the forefront; did he get along well at school, at work; were people deliberately vindictive or was his neighbor just? What was his emotional life like? When tuberculosis was diagnosed what impression did it make upon him; was this mental imprint permanent or had it been altered; if so, in what manner? In what way had his disease manifested itself upon his composure? Was he irritable at the time tuberculosis was diagnosed, before or after the initial signs and symptoms of the disease? In what way did he show an abnormal reaction to the formerly tolerated situations of life? Were any neurasthenic symptoms present? (These symptoms were inquired for in detail.)

The patients' replies were recorded, and an attempt was made to extend these subjective data by observing the patient on the ward daily; noting his attitude toward physicians and patients; the type of questions he asked and the interest he displayed in his case. The patient's viewpoints, regarding his fears and hopes for the future, were also inquired into.

In a former study, undertaken in the Institute for Mental Diseases, Howard, Rhode Island, it was found that tuberculosis occurred in 12 per cent of the patients who had lived within the sanatorium for years, whereas in the new arrivals only 2 per cent had pulmonary tuberculosis.

Dementia praecox was the mental disease diagnosed in 60 per cent of the tuberculosis patients. Fifty-one histories, of the 75 tuberculosis patients found, gave adequate information concerning the presence of tuberculosis and insanity in the families of these cases. Twenty-four patients gave a family history of mental disease; 14 patients had pulmonary tuberculosis in their families, in 11 cases of which the tuberculosis was present in the immediate relatives, involving as many as five members in one family.

Three hundred and thirty-eight histories of nontuberculous patients were then examined in reference to the presence of tuberculosis and insanity in the family. Thirty-four cases had neither disease present; in 191 cases insanity was present in the family; in 54 cases tuberculosis was present; in 52 cases of which it was present in the immediate family and in 43 cases both insanity and pulmonary tuberculosis were present in the family.

Of the 100 tuberculous patients studied in the William H. Maybury Sanatorium, 59 were American-born, 5 were Polish, 5 Jewish, 4 Irish, 3 Scotch, 6 Germans, 5 Syrians, 3 English, 2 Austrian, 3 Swedish, 3

Russians, and 2 were Canadians. The average age of the group was 31 years. Seventy-one per cent of the patients had far advanced, 20 per cent had moderately advanced, and 9 per cent had minimal pulmonary tuberculosis.

Forty patients exhibited neurasthenic symptoms; 80 per cent of this group had far advanced, 5 per cent had moderately advanced, and 15 per cent had minimal pulmonary tuberculosis. There was comparatively little difference in the extent of the disease between the group displaying neurasthenic symptoms and the one free from mental stigmata.

In association with pulmonary tuberculosis, two of the 100 patients had cerebrospinal syphilis, one had mitral stenosis, one bronchiectasis, one bronchial asthma, one diabetes, one chronic arthritis, one chronic interstitial nephritis, one hyperthroidism, and one had cholilithiasis.

Forty-four patients had a "shut-in" character, the remaining fifty-six were sociable and "good mixers."

The types of personality met with may be described as (1) the rebellious, (2) the phlegmatic, (3) the pessimistic, (4) the optimistic, and (5) the restless, apprehensive.

Group 1 consisted of 22 patients, and group 2 numbered sixteen. There were 12 in group 3, 7 in group 4, and 43 in group 5.

B. H. belongs to type one. The chief features characterizing his stay here were insubordination and a quarrelsome disposition. He was always at odds with his environment in his early youth; a recluse. He obeyed the impulse of the moment; distrusted everyone, was restless, and often contemplated suicide. At this sanatorium he displayed these characteristics unaltered. Tuberculosis, in his case, was merely a concurrent physical ailment.

W. K. belongs to type two. His chief characteristics in this hospital were his placidity, obedience and seclusiveness. As a child he preferred the woods to companionship; was introspective; yet made an attempt to face reality by forcing himself to be a mixer. He succeeded partially, whenever necessary, in this distasteful task. He sought refuge in phantasy formation. At the sanatorium he kept to himself; never spoke, unless spoken to, and then was very brief in his answers. He coöperated well with the physicians and was a compliant patient: he died within a few weeks of the onset of severe, repeated haemoptyses. He regarded this ominous event with the equanimity which had characterized his general reaction to life. *Der Mensch stirbt in seinem Character.*

T. B. belongs to type three. Although his pulmonary tuberculosis is improving rapidly, he is worried; is dissatisfied with his life here; fears the future and cannot be reassured; is continuously asking trifling questions which

appear momentous to him and he repeats them often on the succeeding visits of the physician. He is introspective and asocial. As a child he was seclusive and a victim of phobias, which persisted for years; then, as now, he suffered from insomnia. He distrusted people in his youth, an attitude he at present also possesses; he thought that they were deceiving him; felt that he was inferior. He could not get along with people; was very unstable emotionally. The reactions of the tuberculous man in his case are those of the physically healthy boy he once was. He is a petty Hamlet racked by indecision.

A. S. represents type four. He is very popular in this hospital. He is sociable and a "good mixer;" looks upon the future, when he has time for a glimpse into this sphere, with certainty and belief in his recovery, although he bases his assurance upon an inadequate foundation; he is losing ground steadily. He is never despondent and his emotional life maintains an even optimistic level. He has recently had an haemoptysis, but he looked upon this event as a trivial occurrence and ignored it. His first question was, "When do I go to meals?" and not "What is the significance of this haemorrhage?" a question that patient 3 would undoubtedly have asked. As a child the patient always avoided unpleasant scenes; family quarrels, although frequent, did not mar his happiness; he would run into the streets and forget himself in play. The death of four sisters within four years, from pulmonary tuberculosis, although an unpleasant fact, was not an emotional disaster to him. He very soon forgot his grief in the companionship of friends. We see in this case also that "the child is father of the man."

There is the case of the young introspective medical student, whom one may classify as of type 5; who, despite a poverty-stricken youth, which he often dwelt upon minutely and which had made a lasting impression upon him, had almost succeeded in becoming a physician, when tuberculosis overtook him and shattered his hopes. He knew the significance of the disease; he realized his poor prognosis; like Tantalus he had had that which he most desired taken from him, and he was correspondingly embittered. He railed against man and the Fates. Never one to take defeat, he attacked tuberculosis with the energy with which he had combated poverty. He asked persistently and impatiently for pneumothorax; this procedure failed and he daily urged thoracoplasty, which was performed. His vindictive moods severed close friendships, and he went from one hospital to another seeking determinedly for the health that evaded him. He fought to the last, his battle colored by the inherent tendencies which had characterized his youth.

It is thus seen that tuberculosis may bring to light inherent characteristics, but does not alter the personality of the individual.

Sixty of the patients examined did not manifest any neurasthenic symptoms before or during their attack of pulmonary tuberculosis. Their behavior

remained unaltered. They suffered from an involvement of the lungs alone, and their nervous system, with special reference to the psychic level, remained unscathed. In others, however, tuberculosis was characterized by a heightened irritability, an inability to get along with former friends; by stubbornness, restlessness, dislike of former pursuits; by an increasing seclusiveness, lack of strength, malaise, insomnia, fatigue; sleep failed to rest; depressions occurred more frequently; pains appeared in the shoulders, arms, chest; a lack of ambition was noted in certain patients, a heightened activity in others. These symptoms varied often directly with the ebb and flow of the disease; a diminution in the intensity of their tuberculosis produced a correspondingly diminished neurasthenia. Sixteen patients suffered from insomnia; ten had pain in the back; fifteen complained of gastrointestinal disturbances although a fluoroscopic examination failed to reveal intestinal tuberculosis. Nineteen complained of easy fatigability, twenty-four were restless, twenty suffered from difficulty in fixing their attention, thirty-five were afflicted with emotional instability, thirty-two were depressed, and thirty-one were burdened with anxiety. In one patient, K. M., neurasthenic symptoms appeared three years before the onset of the symptoms of pulmonary tuberculosis.

Only one case, E. M., manifested a stormy mental onset with his tuberculosis. He was last in perfect health the winter of 1925; he then had what he calls a severe nervous breakdown. One month before his "nervous breakdown" he was hard to get along with, he claims. Things which previously did not affect him made him lose control of himself; he was irritable. An argument at home, an occurrence which had never bothered him before, made him snap, he said, and he had to go away by himself. He became sick at his stomach, went to pieces (his own words), thought his left hand was paralyzed; his right leg, he insists, was paralyzed. His knees felt numb. He could not control the motions of his left hand, and had involuntary movements of his body; he twisted and turned in every shape going, he maintains. He does not remember whether this state existed for three days or two weeks. He was watched by people, to see that he did not fall out of bed. He lost fifteen pounds during this illness, and never recovered his strength afterward. Two months after his "nervous breakdown" he began to cough; he had an haemoptysis one month after the onset of his cough.

The results of these studies lead to the conclusion that there is no definite relationship between dementia praecox and pulmonary tuberculosis. The praecox develops as a rule upon the basis of a seclusive personality and yet only 44 per cent of the tuberculosis patients examined were of the "shut-in" type. But the question, What accounts for the large percentage of tuberculosis in patients in hospitals for mental disease, especially those having dementia praecox? will be asked. This may be

answered by saying (1) that once a case becomes a praecox it usually means progressive deterioration and apathy, and hence, confinement within walls for the rest of the patient's life. The patients suffering from manic depressive psychoses spend only a comparatively short time within the sanatorium. The general paralytic rarely lives for more than five years, whereas the praecox may spend as much as thirty years within the hospital and often sinks to a vegetative state.

The mode of life has much to do with the development of tuberculosis in the mentally ill, especially those suffering from dementia praecox.

As regards the hereditary relationship between dementia praecox and tuberculosis it was found that among the nontuberculous, mentally diseased patients, 56 per cent had mental disease in the family, while 15 per cent had pulmonary tuberculosis present in their immediate family.

Among the patients whose mental disease was complicated by pulmonary tuberculosis 46 per cent had insanity present in their family, and 21 per cent had tuberculosis also present in the immediate family.

It is thus seen that there is not much difference in the hereditary relationship between the mentally diseased patients who have pulmonary tuberculosis and those who have not.

It is true that a psychotic patient may have as many as five brothers and sisters suffering from pulmonary tuberculosis, but there are many tuberculosis patients who are mentally well and who can show as many phthisical relatives in their immediate family.

Tuberculosis complicates the lot of the psychotic individual, and cannot be held to task for the production of dementia praecox.

George Draper (22) contends that disease arises from the interplay of dynamic forces inherent in the individual and present in the world about him; this viewpoint applies equally well to the mental and physical elements of humanity which are inextricably linked.

The tuberculosis patient is not a being compounded of a few vices or virtues, selfishness, lack of self control, or, on the other hand, optimism and amiability; he is not a character out of Dickens or Ben Jonson, but a human being whose reactions to tuberculosis are essentially his general response to life and its difficulties. The phlegmatic patient remains placid to the end; the optimistic boy regards his tuberculosis in the light that he viewed the troubles that failed to cloud his youthful horizon. The seeking, battling, egotistical student defied and struggled with his tuberculosis as he did with poverty, and the only difference was that in the former affliction he was defeated. Pulmonary tuberculosis brings to

light inherent characteristics. It accentuates the mental traits of the patient, but it cannot produce a psychopathology of its own.

It has been claimed that tuberculosis exerts a toxic action upon the mind, but so does alcohol, and yet the influence of this drug can only manifest itself in definite channels, those which have been laid down for it by the inherent characteristics of the alcoholic. Alcoholic psychoses have been diagnosed in many cases which turned out later to be dementia praecox. The alcohol merely revealed the inherent traits of the individual and was blamed for mental tendencies which it had only disclosed.

It is true that a patient failing rapidly from pulmonary tuberculosis may maintain a secure confidence in his ability to regain his health. He is optimistic, but this mood is due, not to the specific tuberculous toxin, but to different factors. Tuberculosis is often marked by its remissions and exacerbations; a flare-up which frightens the patient is often succeeded by a subsidence in the disease and gives the patient hope. He assumes that because he has overcome one exacerbation that he will successfully triumph over succeeding ones. His ship that has overridden one storm will withstand future ones and will take him to a safe harbor.

A case that often appears to be optimistic on the surface reveals a weakness in this protective mood, on being put to the proof.

The optimist may not be aware seemingly of his serious condition, and it is thought advisable to convey him from the convalescent ward back to the sick ward. Upon being notified of this fact, he is greatly perturbed, although he has been reassured that upon improvement in his health he will be transferred back, and that he will be given more attention in the infirmary because of greater facilities. He protests, often, although he knows that it is for the best that he be transferred, yet he clings tenaciously to his hold on the optimistic mood which he dare not relinquish; it means so much to his peace of mind. He will offer inadequate excuses so that he may remain in the ambulant ward. He fears the infirmary, and transference there means to him his death-warrant. He will say that the suffering that exists in the infirmary distresses him, that the sight of people dying makes him feel wretched, or that the thought of going to the infirmary disheartens him. He offers any excuse, in order to avoid too intimate a contact with the dread spectre of tuberculosis. The optimism of the tuberculosis patient has been unduly stressed because it appears incongruous that a person so near death should speak with certainty of a nebulous future. The

character of the patient was moulded long before tuberculosis entered the field, and it, and not phthisis, determines his mental reactions.

There is the case of H. P. who was always introspective and is abnormally religious, almost a zealot. He is firmly convinced that disease is due to transgression and therefore seeks solace in the thought that when he will have expiated his sins he will once more regain his health. By this devious route H. P. has obtained comparative solace and a certain amount of optimism, although he admits that he has always taken life seriously and that he is continually struggling to reassure himself, hoping that he will get well; and he has accordingly built up his rationalistic views to shelter himself from the unpleasant truth. He seeks to reassure himself, a characteristic which is not peculiar to tuberculosis patients alone, but is found throughout mankind.

There are cases thoroughly ingrained with the principles of Christian Science. They derive an optimism from this extraneous source. Others, although they do not declare allegiance, admit that they receive comfort and assurance from its persuasive and soothing doctrines.

Tuberculosis is only one of different diseases that produce neurasthenic symptoms. Many tuberculosis patients are not disturbed by neurasthenia during any phase of their disease. One cannot diagnose tuberculosis by the concomitant mental phenomena alone, and therefore one is not warranted in speaking of a definite psychopathology of pulmonary tuberculosis.

Tuberculosis resembles alcohol and paresis in its influences on the mind. It can only act upon the soil prepared for it; it can only influence inherent characteristics.

SUMMARY

1. There is no definite relationship between insanity and tuberculosis, nor is there a peculiar affinity between dementia praecox and pulmonary tuberculosis. The mode of living determines the large incidence of phthisis in hospitals for mental disease.

2. Pulmonary tuberculosis does not alter the personality of the patient. It merely influences inherent tendencies and exposes the true individual. There is no one type of personality characteristic of pulmonary tuberculosis.

3. The neurasthenia found in tuberculosis is not characteristic of this disease alone. It is often absent.

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A CLINICAL STUDY OF TUBERCULIN FRACTIONS PREPARED FROM NONPROTEIN CULTURE MEDIA[1]

FREDERICK EBERSON[2] AND ERNEST WOLFF[3]

In previous experimental and clinical studies (1) published during 1925–1927, one of us (F. E.) has stressed the inadequacy of the Old Tuberculin test material and questioned its diagnostic value. Moreover, it is felt that, despite the frequent contributions to the subject of tuberculins and their diagnostic properties, a certain type of detailed analysis of groups of patients has not been reported in the literature.

An exhaustive clinical and statistical analysis of the observed facts is therefore presented in this report. In this comparative study of skin reactions made with Old Tuberculin and with a fraction of tuberculin prepared from a synthetic nonprotein culture medium in which tubercle bacilli had been cultivated, are embodied the results of an investigation that is now in its fifth year. The apparent advantage of this modified tuberculin for diagnostic purposes is its freedom from nonspecific irritating components and from protein materials that are unrelated to the tubercle bacillus itself.

As might be expected, certain tuberculin components have their homologues in the fractions isolated from tubercle bacilli by chemical methods similar to or identical with those used for tuberculin studies.

Recently, the coöperative investigations conducted by the National Tuberculosis Association have confirmed and extended much of the earlier work published on the chemical analysis of tubercle bacilli and tuberculins. Notably Johnson (2), Anderson (3), Long and his associates (4), Petroff (5), and others have made valuable contributions in this field. Prior to these investigators Goris (6) in 1920 had already

[1] This investigation was aided, in part, by a grant from the San Francisco Tuberculosis Association and the California State Tuberculosis Association. Read in abstract before the Pathology and Bacteriology Section of the California State Medical Association, at its 57th annual session held at Sacramento, California, May 2, 1928.

[2] Department of Medicine, University of California Medical School, San Francisco, California.

[3] Department of Pediatrics, University of California Medical School, and the George Williams Hooper Foundation for Medical Research, San Francisco, California.

shown by extensive chemical studies of tubercle bacilli that a phosphatide could be isolated having specific properties. This substance is identical with that described by Anderson recently. It has been isolated also from tuberculin prepared from nonprotein culture media and possesses specific diagnostic properties (7). Goris has also referred to alcohol-insoluble substances derived from tubercle bacilli. These have been found in tuberculin and reported during the past few years (4) (7). The relation of acid-fastness to certain lipoidal constituents, shown by Goris, was confirmed three years later by Long (8).

Other studies related to analysis of the tubercle bacillus and tuberculin have been published by Nègre (9), Boquet (10), and Massias (11), antedating confirmatory work by Pinner (12), Long (4), Anderson (3), Zinsser (13), Mueller (14), and others. Especially interesting was Boquet's findings of a specific lipoidal element in tubercle bacilli. This confirmed the observations of Goris and later was again substantiated by Long.

Application of the principles of bacteriological and chemical analysis to large-scale production of tuberculin has been suggested naturally as the outcome of the numerous contributions that have been cited, and has been emphasized especially by Johnson (2).

It is believed that comparative studies similar to those we have been advocating and have reported here may aid in correlating laboratory and clinical data on tuberculins or similar products to be used for diagnosis or therapy.

PREPARATION OF TUBERCULIN FRACTIONS[4]

A moderately virulent strain of human tubercle bacilli was grown in a substrate containing ammonium succinate, dipotassium phosphate, magnesium sulphate, calcium chloride and distilled water, with a pH value of 7.0. The media, originally described by Gessard and Vaudremer (15), were tested in different H-ion concentrations and modified by one of us (*loc. cit.*). After six weeks' incubation at 38.0°C., 1500 cc. of the material were evaporated to one-tenth volume and the fractions secured from it. A weighed volume was added to 19 volumes of pure methyl alcohol to effect complete precipitation, and filtered. To the filtrate, containing washings of methyl alcohol derived from the alcohol-insoluble fraction, were added four volumes of pure ethyl ether, and a second frac-

[4] For the preparation of generous supplies of these materials and coöperation, acknowledgment is made to Eli Lilly & Co., (Biological Department), Indianapolis, Indiana.

tion separated by filtration. The precipitate was washed thoroughly with ether and the combined filtrates evaporated virtually to dryness to yield the third fraction.

The alcohol-insoluble fraction (T.E.) represented 5.17 gm. of precipitate and was taken up in 45 cc. of salt solution, each cubic centimetre containing 114.9 mgm. of material. The ether-insoluble portion represented 2.4 gm. of precipitate in a volume of 45 cc. of salt solution, making 53.3 mgm. per cc. The ether-soluble fraction represented 1.295 mgm. of precipitate in 15 cc. of salt solution, or 86.3 mgm. per cc. All the materials were preserved with 0.25 per cent ether-tricresol.

The alcohol-insoluble fraction represented 3.44 per cent by weight of the original tuberculin, the ether-insoluble fraction 1.6 per cent, and the ether-soluble 0.86 per cent. For clinical tests the fractions were diluted so that 1 cc. contained 1.0 mgm. of tuberculin material.

In the present investigation only the results obtained with T.E. will be reported. The ether-insoluble fraction, a phosphatide derivative, also gave specific skin reactions. A preliminary statement of the chemical analysis and results obtained with this phosphatide (16) was published in 1925, and clinical tests were described in subsequent reports (*loc. cit.*).

Numerous substrates for the preparation of tuberculin have been described in the literature. With minor modifications these materials have differed chiefly in the names of the writers associated with the adaptations. Among these Kühne (17) in 1894, Ruppel and Rickmann (18) in 1910, Löwenstein and Pick (19) in 1911, Gessard and Vaudremer (15) in 1922, and Long (20) in 1924, have published reports on "synthetic media" for tubercle bacilli. Excepting that of Gessard and Vaudremer, all the other substrates contained asparagin as a base, with slight modification in the content of citric, ammonium, phosphoric, potassium or sodium salts. The medium described by Gessard and Vaudremer should appeal to one because of its simplicity and ease and cheapness of preparation, containing but four ingredients as compared with the seven and eight of other writers. One of us (F.E.) has confirmed the observation that glycerine is not indispensable for growth with the simplest of media, although 1 to 2 per cent by volume favors growth of the tubercle bacillus and ensures acid-fastness which may be lost almost completely after one transplant when glycerine is not present.

CLASSIFICATION OF CLINICAL MATERIAL

In studying the efficacy of test materials, it is not sufficient to compare the skin reactions without reference to some basic standard. It would seem more important to analyze the observed discrepancies in terms of a carefully evaluated group of clinical symptoms, signs, and auxiliary laboratory data, and to refer the observations to the patient, who must always be considered as the standard.

The diagnosis of juvenile tuberculosis presents many difficulties of which the greatest, perhaps, lie in that large borderline group of patients having symptoms and signs generally rendering a patient a tuberculosis suspect. There is doubt, however, whether the so called symptom-complex of tuberculosis in childhood is by any means a fixed quantity, and whether, as such, it can be used as a basis for certain diagnosis. An attempt was made, therefore, in our study to subject all the available data to an exhaustive analysis with the aim of correlating, wherever possible, the numerous variables most likely to confuse the picture. By this method we were able to compare the different skin reactions in terms of definite variables that occurred in the fixed groups chosen for study.

Our classification, as a point of departure, was based upon the complete clinical examination, history and X-ray findings, with the results of Old Tuberculin tests as a tentative gauge for comparison with the tuberculin fractions.

Symptoms: The items considered were loss of weight, or failure to gain, lack of appetite, fatigability, cough, night-sweats, lassitude, nervousness and elevation of temperature.

Clinical Findings: The points considered were malnutrition, tuberculous lymphadenitis, involvement of the bones and cervical lymph nodes, phlyctenular processes and percutory and auscultatory findings.

DIAGNOSIS AND CLINICAL IMPRESSION

The tuberculous group comprised pulmonary tuberculosis, tuberculosis of the bronchial lymph nodes, tuberculous cervical adenitis, healed primary focus, tuberculosis of bones and peribronchial tuberculosis. The nontuberculous group included enlarged bronchial lymph nodes, nontuberculous pulmonary disease, clinically normal patients, the three named having positive tuberculin tests (O.T.), and a group with negative tuberculin tests and likewise free from tuberculous manifestations.

In all the groups attention was paid to associated diagnoses in every

case, so that the possible effect of complicating clinical conditions upon tuberculin reactions might be properly interpreted.

Roentgenographic Findings: Chest films were diagnosed under the headings of primary focus, calcified bronchial lymph nodes, hilum calcification, peribronchial infiltration, enlarged bronchial lymph nodes, increased bronchial markings, parenchymal tuberculosis, thickened interlobar pleura, thickened apical pleura, and negative.

Contact and Noncontact History: The history of definite exposure to and contact with tuberculosis was ascertained as accurately as possible. It is evident that the greatest source of error is found in the so called noncontact case, owing to our inability to confirm this point in children beyond the nursery age. For practical purposes, however, this division into two groups may be of interest if it be not of definitely proved value.

INTRACUTANEOUS TUBERCULIN TESTS

Comparative tests were made with human Old Tuberculin and tuberculin fraction (T.E.), using a fixed dilution equivalent to 0.1 mgm. of tuberculin substance. Suitable controls were made with salt solution and culture media from which the tuberculins had been prepared. The simultaneous injections were observed at 24-, 48- and 72-hour intervals, and in most cases until the visible skin reaction had disappeared. The areas were measured and the degree of infiltration and reddening noted. For roughly quantitative purposes, the reactions were classified as follows:

A: Doubtful test, with area less than 0.5 by 0.5 cm., without reddening or infiltration, and fading within 24 hrs.
B: Slightly positive test, with area 0.5 by 0.5 to 1.0 by 1.0 cm., without definite reddening or infiltration or with slight reddening only, and persisting 24 hours.
C: Moderately positive test, with area 1.0 by 1.0 cm., with slight to moderate reddening and infiltration, and persisting 48 hours.
D: Strongly positive test, with area 2.0 by 2.0 cm. or more, with profound reddening and infiltration, and persisting more than 48 hours.
Negative: Areas too small and too transitory to be considered under the doubtful group A.

The skin reactions were classified further with reference to agreement or disagreement of the comparative tuberculin and fractional tests. Five subdivisions were made.

1: Old tuberculin negative, and fraction positive
2: Old tuberculin positive, and fraction negative
3: Old tuberculin same as fraction
4: Old tuberculin weaker than fraction
5: Old tuberculin stronger than fraction

In each of these groups, the preceding grades of reaction (*A*, *B*, *C*, *D*, *Neg.*) were noted, so that every possible relation of one test to the other might be visualized.

We were able in the majority of patients to study comparative reactions for two to three years and in a considerable number for four years.

1: Tuberculosis of Bronchial Lymph Nodes

In this group of 27 contacts and 12 noncontacts was represented a healed condition, to which 31 cases definitely belonged, under the heading of healed bronchial lymph-node tuberculosis without any other manifestations.

The skin reactions with O.T. were greater than tuberculin fraction in 23, or 59 per cent, of all the cases, and of these there were 2 that showed a positive O.T. test when the test with the fraction was negative. Of these two patients, one was clinically normal and had enlarged bronchial lymph nodes with some calcification, and the other had enlarged lymph nodes that were not indubitably tuberculous.

In the group of 31 patients (healed and without any other manifestations) 18 reacted more strongly to O.T. than to tuberculin fraction, and of these tests 14 were strong, that is, *D* and *C*, of which 11 were *D*. Included in the series were 2 that reacted positively to O.T. when the test with tuberculin fraction was negative. Of the reactions with the fraction giving a stronger test than O.T. 3 were doubtful and 2 were weakly positive.

The results showed that 20 tests were definitely or strongly positive to O.T. when the fraction gave doubtfully positive, weak or negative reactions. When the tests with O.T. and fraction were the same, 4 of the 8 cases in this group gave strong reactions, 3 moderate and 1 slightly positive.

On the basis of the observations made in this group of patients it would appear that the O.T. gave less information as compared with the tuberculin fraction (T.E.).

2: Enlarged Bronchial Lymph Nodes

In this group were considered:

A: Enlarged bronchial lymph nodes with positive O.T.
B: Enlarged bronchial lymph nodes associated with healed bronchial lymph-node tuberculosis

TABLE 1

Tuberculosis of bronchial lymph nodes

CONTACTS	NONCONTACTS	TOTAL	SKIN REACTIONS
14	7	21	O.T. greater than tuberculin fraction (>)
5	0	5	O.T. smaller than tuberculin fraction (<)
2	0	2	O.T. positive, tuberculin fraction negative (+)
6	5	11	O.T. equal to tuberculin fraction (=)
27	12	39	Total

Comparative skin tests and degree of reaction

SUBGROUP		>				<			+			=					
			D	C	B	A	B	C	D	C	B	D	C	B	A	Negative	
A	Contact	1	1														2
	Noncontact	1											1				
B	Contact	0															1
	Noncontact	1	1														
C	Contact	1	1														2
	Noncontact	1										1					
D	Contact	2	1									1					2
	Noncontact	0															
E	Contact	0															1
	Noncontact	1	1														
F	Contact	23	8	1	2	3	2			1	1	3	1	1			31
	Noncontact	8	3	2								1	2				
Total.....		39	21			5			2			11					39

A: Tuberculosis of bronchial lymph nodes (active) with pulmonary involvement.
B: Tuberculosis of bronchial lymph nodes associated with tuberculous cervical adenitis.
C: Tuberculosis of bronchial lymph nodes associated with tuberculosis of bones.
D: Tuberculosis of bronchial lymph nodes associated with primary focus.
E: Tuberculosis of bronchial lymph nodes associated with phlyctenular process.
F: Tuberculosis of bronchial lymph nodes (healed and without other manifestations).

C: Enlarged bronchial lymph nodes associated with tuberculous cervical adenitis

D: Enlarged bronchial lymph nodes associated with healed peribronchial tuberculosis

TABLE 2

Enlarged bronchial lymph nodes

CONTACTS	NONCONTACTS	SKIN REACTIONS	TOTAL
13	7	O.T. greater than tuberculin fraction (>)	20
9	6	O.T. smaller than tuberculin fraction (<)	15
7	5	O.T. positive, tuberculin fraction negative (+)	12
14	11	O.T. equal to tuberculin fraction (=)	25
43	29	Total.....	72

Comparative skin tests and degree of reaction

SUBGROUP			>			<			+			=				
			D	C	B	A	B	C	D	C	B	D	C	B	A	Negative
A	Contact	36	6	3	2	4	2	1	2		4	1	2	6	2	1
	Noncontact	25	4	1	1	2	3			1	3	3	3	2	2	
B	Contact	2					1			1						
	Noncontact	1	1													
C	Contact	2	1	1												
	Noncontact	1				1				1		1				
D	Contact	1										1				
	Noncontact	2														
E	Contact	1										1				
	Noncontact															
F	Contact	1					1									
	Noncontact															
Total.....		72	20			15			12			25				

A: Enlarged bronchial lymph nodes with positive O.T. test.

B: Enlarged bronchial lymph nodes associated with healed tuberculosis of bronchial lymph nodes.

C: Enlarged bronchial lymph nodes associated with tuberculous cervical adenitis.

D: Enlarged bronchial lymph nodes associated with healed peribronchial tuberculosis.

E: Enlarged bronchial lymph nodes associated with phlyctenular processes.

F: Enlarged bronchial lymph nodes associated with tuberculosis of bones.

E: Enlarged bronchial lymph nodes associated with phlyctenular processes.
F: Enlarged bronchial lymph nodes associated with tuberculosis of bones.
G: Enlarged bronchial lymph nodes associated with small calcifications.

In this group 61 of the 72 cases were negative for clinical signs of tuberculosis and, of these, 9 gave complaints such as lassitude, fatigue, and the like. The skin reactions in this group, as shown in table 1, included 17 cases with O. T. greater than fraction, and 10 cases with O.T. positive when the fraction was negative, a total of 27 cases, or 44.2 per cent, with a predominating O.T. test. Of these 27 tests, 17 were moderately to very strongly positive (*C* – *D*).

TABLE 3

Nontuberculous pulmonary disease

CONTACTS	NONCONTACTS	SKIN REACTIONS	>			<			+				-				
			D	C	B	A	B	C	D	C	B	A	D	C	B	A	Negative
3	4	(>) O.T. greater than tuberculin fraction	3	1	3												
0	2	(<) O.T. smaller than tuberculin fraction				1	1	0									
1	6	(+) O.T. positive, tuberculin fraction negative							2	1	4	0					
2	4	(=) O.T. equal to tuberculin fraction											1	2	1	2	0
6	16	Total.....	7			2			7				6				

In contrast, 5 tests with the fractional tuberculin were weakly positive (*B*) and 6 doubtful (*A*), and 6 moderately strong. The tests with fractional tuberculin were stronger than O.T in 12 cases, of which 6 were doubtful, 5 weakly positive and 1 moderately positive. In cases with symptoms that might be construed as those of tuberculous activity it is noteworthy that the tuberculin fractions did not give negative tests when the O.T. tests were correspondingly positive. (Table 2.)

3: Nontuberculous Pulmonary Disease

This series included 22 patients classified as positive to O.T. and having nontuberculous pulmonary disease. There were 14 cases in which O.T. gave either a greater reaction than the fraction, or was positive when the fraction was negative. Sixteen cases out of twenty-two in the

entire group were noncontacts, among which were ten with O.T. predominating or positive when the fraction was negative. When O.T. was stronger, reactions with fractions were doubtful in 5 instances (*A*), slightly positive (*B*) in 2, and, by contrast, the O.T reactions were marked (*D*) in 3 cases, definitely positive (*C*) in one, and slightly positive (*B*) in three.

In all the cases in which fractions gave reactions equal to O.T., showing medium or strong reactions, or in the cases in which fractions gave medium to strong tests and O.T. at the same time gave weak to doubtful results, symptoms and signs were present in the history that might have been attributable to tuberculous activity. This, we believe, would appear to be of some significance. (Table 3.)

4: Clinically Normal Group

This group was divided into (*A*) clinically normal, without pathological changes, but with a positive tuberculin test; (*B*) clinically normal, with small hilum calcifications and positive O.T.; and (*C*) clinically normal, with definite signs of healed tuberculous disease.

Ten out of 25 of this clinically normal *A* group gave greater reactions with O.T. than with fractions, and in 2 cases, in addition, positive tuberculin tests were obtained when fractions reacted negatively. It may be noted that in this group of 12, seven were contacts and 5 noncontacts. In the entire group of 25, fourteen were contacts and 11 noncontacts.

Group B: Five out of 11 gave a greater reaction with O.T. than with fractions and in addition 3 cases were positive when fractions were negative. In this group of 11, two cases were contacts and 9 noncontacts, and in the group of eight reactors, one was a contact and seven were noncontacts.

Group C: Four out of 7 in this group gave a greater reaction with O.T. than with fractions. In this group of 4, one was a noncontact and 3 were contacts.

The clinical group as a whole, numbering 43 cases, was divided almost equally between contact and noncontact patients, there being 22 of the former and 21 of the latter.

In all, 24, or 55.8 per cent, of the tests gave stronger reactions with O.T., and included 5 that were positive when the corresponding tests with the tuberculin fraction were negative. In 50 per cent of these the

reactions were classed as *D*. It is noteworthy that the more marked O.T. reactions occurred in those groups (*A* and *B*) in which either pathological changes or signs of healed tuberculous disease were not present. This was observed in 46.5 per cent of the total number of cases and in 83.3 per cent of the tests in which the O.T reacted more strongly.

TABLE 4

Clinically normal

CONTACTS			NONCONTACTS			SKIN REACTIONS	TOTAL
A*	B	C	A	B	C		
6	1	3	4	4	1	O.T. greater than tuberculin fraction (>)	19
2	0	1	2	1	2	O.T. smaller than tuberculin fraction (<)	8
1	1	0	1	2	0	O.T. positive, tuberculin fraction negative (+)	5
5	1	0	4	1	0	O.T. equal to tuberculin fraction (=)	11
14	3	4	11	8	3	Total.....	43

Comparative skin tests and degree of reaction

SUBGROUP*	>			<			+				=					TOTAL
	D	C	B	A	B	C	D	C	B	A	D	C	B	A	Negative	
A	5	2	3	1	1	2	0	0	1	1	3	1	5	0	0	25
B	3	2	0	0	1	0	2	1	0	0	1	0	1	0	0	11
C	2	1	1	1	2	0	0	0	0	0	0	0	0	0	0	7
Total....	10	5	4	2	4	2	2	1	1	1	4	1	6	0	0	43

**A:* Clinically normal without pathological changes, but with a positive tuberculin test.
B: Clinically normal with small hilum calcification and positive tuberculin test.
C: Clinically normal with definite signs of healed tuberculous disease.

Inasmuch as this group comprises cases with tuberculous infection but without any active process, the marked O.T. reaction gives information that is not consistent with the clinical picture. We are more concerned in a group of this type with the relation that the test might bear to the significant clinical data. In this connection the lesser reactivity of the tuberculin fraction might appear to have more significance, particularly when negative results give more information. (Table 4.)

5: Negative Tuberculin Test

In this group of 17 cases with negative O.T. reactions, 10 were likewise negative with fractional tuberculin. Of the remaining 7, three gave a doubtful test, 2 a weakly positive and 2 (contacts) gave a strong reaction. In addition, these 2 patients showed a record of a positive O.T. test in the previous history. In all these cases symptoms and signs were present, suggesting a possible old infection. (Table 5.)

TABLE 5

Negative tuberculin test

	O.T. NEGATIVE; TUBERCULIN FRACTION NEGATIVE	O.T. NEGATIVE; TUBERCULIN FRACTION POSITIVE				SIGNIFICANT FINDINGS
		A	B	C	D	
Contact	5	0	0	0	2	Cough, lassitude and thickened apical pleura
						Cough, night-sweats, lassitude, fatigue, loss of weight, loss of appetite, positive percussion and auscultation
Noncontact	5	3	2	0	0	Postpneumonia, bronchiectasis, loss of weight
						Night-sweats, cough, loss of weight
						Cough, loss of weight, night-sweats, fatigue, loss of appetite, positive percussion and auscultation
						Primary focus and peribronchial infiltration
						Lassitude, night-sweats, tubercle bacilli in sputum, cough

6: Pulmonary Tuberculosis and Peribronchial Tuberculosis

In these groups, numbering 20 patients, differentiating characteristics of the test substance suggested that the reaction with the tuberculin fraction was better correlated with the clinical findings. In a group of 5 patients, for example, the reaction with O.T was smaller than with the tuberculin fraction. Among these were found 3 cases of pulmonary tuberculosis, one of which was associated with a pleuritic effusion, and 2 cases of peribronchial tuberculosis, associated in one instance with tuberculosis of the bones. However, since these groups were too small for detailed study and correlation it did not seem advisable to draw any rigid conclusions. In our opinion the value of a comparative study with

TABLE 6

Pulmonary tuberculosis and peribronchial tuberculosis

DIAGNOSIS	ASSOCIATED DISEASE	CONTACT	NONCONTACT	SKIN TEST (LETTERS INDICATE DEGREE OF REACTION FOR SUBSTANCE USED IN TEST)
Pulmonary tuberculosis		+	−	O.T. smaller than tuberculin fraction (C D)
do	Enlarged bronchial lymph nodes (healed)	+	−	O.T. greater than tuberculin fraction (D B)
do	do	−	+	O.T. equal to tuberculin fraction (B)
do	do	−	+	O.T. greater than tuberculin fraction (D B)
do		+	−	O.T. greater than tuberculin fraction (D A)
do	Enlarged bronchial lymph nodes	−	+	O.T. greater than tuberculin fraction (D B)
do	do, and pleurisy with effusion	+	−	O.T. smaller than tuberculin fraction (C D)
do		+	−	O.T. positive, tuberculin fraction negative (D)
do		+	−	O.T. positive, tuberculin fraction negative (B)
do		+	−	O.T. equal to tuberculin fraction (D)
do		−	+	O.T. positive, tuberculin fraction negative (C)
do		+	−	O.T. smaller than tuberculin fraction (C D)
Peribronchial tuberculosis	Enlarged bronchial lymph nodes	+	−	O.T. greater than tuberculin fraction (D C)
do, inactive		+	−	O.T. greater than tuberculin fraction (C B)
do, healed	Tuberculosis of bone (healed)	−	+?	O.T. smaller than the tuberculin fraction (B C)
do, do	Tuberculosis of bronchial lymph nodes	+	−	O.T. greater than tuberculin fraction (B A)
do	Enlarged bronchial lymph nodes	−	+	O.T. equal to tuberculin fraction (C)(1926) O.T. smaller than tuberculin fraction (A B) (1927)
do	do	−	+	O.T. positive, tuberculin fraction negative (C)
do	Questionable pulmonary tuberculosis	+	−	O.T. equal to tuberculin fraction (D)
do	Phlyctenular process and enlarged bronchial lymph nodes	+	−	O.T. equal to tuberculin fraction (D)

Résumé of skin reactions in 20 patients

	PULMONARY TUBERCULOSIS	PERIBRONCHIAL TUBERCULOSIS
O.T. greater than tuberculin fraction	4	3
O.T. smaller than tuberculin fraction	3	2
O.T. equal to tuberculin fraction	2	2
O.T. positive, tuberculin fraction negative	3	1

the test substances under consideration can be better determined by devoting attention to the clinical groups of patients presenting vague or indefinite clinical conditions that might be mistaken for tuberculosis. (Table 6.)

7: Tuberculous Cervical Adenitis

In this group of 25 patients with definite evidence of tuberculous infection and healed tuberculous disease, including 8 tuberculous cervical adenitis, 6 tuberculosis of the bone and 11 healed primary foci, O.T. gave in all but 4 instances (84 per cent) medium or very marked reactions. The tuberculin fraction (T.E.) gave a medium or strong reaction in 11 cases, or 44 per cent.

TABLE 7

TUBERCULOUS CERVICAL ADENITIS	TUBERCULOSIS OF BONE	HEALED PRIMARY FOCUS	SKIN REACTIONS	TOTAL
6	3	5	O.T. greater than tuberculin fraction	14
0	2	2	O.T. smaller than tuberculin fraction	4
0	0	1	O.T. positive, tuberculin fraction negative	1
2	1	3	O.T. equal to tuberculin fraction	6
8	6	11	Total	25

Concerning a judgment regarding tuberculous infection, the reactions with O.T. showed a satisfactory correlation of the tests with clinical data. From the standpoint of clinical activity or disease, however, the T.E. appeared to outweigh the O.T. as a diagnostic agent. Similar results have been obtained in another series of more than 100 patients with healed primary foci and tuberculous cervical adenitis.

It would follow from our observations that a diagnosis of healed tuberculous cervical adenitis or of a healed primary focus in the lungs cannot be made with certainty in the absence of a definitely marked positive reaction to O.T.

In the following tables the complete results are summarized:

Skin reactions

	O. T. GREATER THAN T. E.	O. T. SMALLER THAN T. E.	O. T. POSITIVE; T. E. NEGATIVE	O. T. NEGATIVE; T. E. POSITIVE	O. T. EQUAL TO T. E.
Tuberculous groups (127)	61 (48%)	22 (17.3%)	12 (9.4%)		32 (25.3%)
Nontuberculous groups (111)	27 (24.3%)	17 (15.3%)	19 (17.1%)	7 (6.4%)	41 (36.9%)

The significance of these comparative skin reactions is evidently in favor of the T.E. when it is remembered that 50 patients, or 39.3 per cent of the entire tuberculous group, represented a clinically healed or clinically normal condition without any other manifestations. Yet the O.T. gave stronger reactions than T.E. in 57.4 per cent of the total number of cases. In the nontuberculous group O.T. gave stronger reactions in 41.4 per cent of the cases, again suggesting an erroneous interpretation of the clinical picture. Similarly, the occurrence of negative tests with T.E. when O.T. was positive pointed again to better correlation on the part of the T.E. with the clinical observations. The tests with T.E. and O.T. were the same in 36.9 per cent of the cases in the nontuberculous group and here also the clinical analyses favored the T.E. as a criterion. Reference to the summaries under the corresponding headings will show these facts in clearer detail.

SKIN REACTION	DOUBTFUL (A) OR NEGATIVE				MODERATELY POSITIVE (C) AND STRONGLY POSITIVE (D)			
	Fraction	Per cent	O. T.	Per cent	Fraction	Per cent	O. T.	Per cent
Tuberculous	14	16.7	3	3.6	38	45.2	66	78.5
Nontuberculous	62	40.0	35	22.5	57	36.8	71	61.7

Comparisons of the tests with tuberculin fraction and O.T indicate that the former gave a doubtful or negative reaction more frequently in the tuberculous group in the ratio of approximately 4.5 to 1, and in the nontuberculous group of 1.7 to 1. A moderately positive to strongly positive reaction was given more frequently by the O.T. in the tubercu-

TABLE 8

Evaluation of skin reactions according to degree and in terms of selective grouping by O.T. and tuberculin fraction among contacts and noncontacts

TOTAL CONTACTS	TESTS WITH FRACTION	PER CENT WITH FRACTION	PER CENT WITH O.T.	GROUP*	TOTAL NON-CONTACTS	TESTS WITH FRACTION	PER CENT WITH FRACTION	PER CENT WITH O.T.
29	19	65.5	34.5	A	21	15	71.4	28.6
66	34	51.5	48.5	B	50	25	50.9	49.1
37	22	59.4	40.6	C	43	22	51.2	48.8
62	18	29.2	70.8	D	47	14	29.8	70.2
24	16	66.7	33.3	Neg.	31	20	64.5	35.5

* A, B, C, D, Negative = degree of skin reaction, respecting doubtful, slightly positive, moderately positive, and intense or negative.

TABLE 9

Distribution of tuberculous and nontuberculous cases according to contacts and noncontacts and degree of skin reaction

SKIN REACTION	FRACTION		DIAGNOSIS	O.T.	
	Contact	Noncontact		Contact	Noncontact
A	6	1	Tuberculous	3	0
	14	14	Nontuberculous	10	6
B	21	11	Tuberculous	11	4
	20	16	Nontuberculous	26	23
C	10	9	Tuberculous	12	7
	19	15	Nontuberculous	17	13
D	15	4	Tuberculous	32	15
	11	12	Nontuberculous	20	21
Neg.	6	1	Tuberculous	0	0
	17	17	Nontuberculous	7	12

Cases tabulated without distinction as to contact or noncontact

TUBERCULIN FRACTION	O.T.	SKIN REACTION	DIAGNOSIS
7	3	A	Tuberculous
28	16		Nontuberculous
32	15	B	Tuberculous
36	49		Nontuberculous
19	19	C	Tuberculous
34	30		Nontuberculous
19	47	D	Tuberculous
23	41		Nontuberculous
7	0	Negative	Tuberculous
34	19		Nontuberculous

TABLE 10

Tuberculous and nontuberculous series of patients with reference to degree of skin reaction and frequency

	O. T. GREATER THAN T. E.			O. T. SMALLER THAN T. E.			O. T. POSITIVE; T. E. NEGATIVE				O. T EQUAL TO T. E.					O. T. NEGATIVE; T. E. POSITIVE				TOTAL
	D	C	B	A	B	C	D	C	B	A	D	C	B	A	Neg.	A	B	C	D	
Tuberculous groups:																				
Tuberculosis of bronchial lymph nodes	16	3	2	3	2			1	1		6	4	1							39
Total		(21)			(5)			(2)				(11)								
Tuberculous cervical adenitis	4	2									1	1								
Tuberculosis of bones	3				2						1									25
Healed primary focus	5				1	1					2	2								
Total		(14)			(4)							(7)								
Pulmonary tuberculosis	4					3	1	1	1		1		1							12
Total		(4)			(3)			(3)				(2)								
Peribronchial tuberculosis	1	1	1	1	1			1			2									8
Total		(3)			(2)			(1)				(2)								
Clinically normal	10	5	4	2	4	2	2	1	1	1	4	1	6							43
Total		(19)			(8)			(5)				(11)								
Total		61			22			11				33								127
Nontuberculous groups:																				
Enlarged bronchial lymph nodes	12	5	3	7	7	1	2	3	7		7	5	8	4	1					72
Total		(20)			(15)			(12)				(25)								
Nontuberculous lung disease	3	1	3	1	1		2	1	4		1	2	1	2						22
Total		(7)			(2)			(7)				(6)								
Negative O.T. group															10	3	2		2	17
Total												(10)					(7)			
Total		27			17			19				41					7			111

lous group in the proportion of 1.7 to 1, and in the nontuberculous group of 1.8 to 1.

The diagnostic significance of the test with the tuberculin fraction becomes more evident in considering that actually only 29.8 per cent of

TABLE 11

DIAGNOSIS	CONTACT	NONCONTACT	DOUBTFUL	O. T. POSITIVE; T. E. POSITIVE	O. T. POSITIVE; T. E. NEGATIVE	O. T. NEGATIVE; T. E. POSITIVE	O. T. NEGATIVE; T. E. NEGATIVE	TOTAL
Hilum and peribronchial tuberculosis	16	2		13	2(a)	2	1	18
Mediastinal tuberculosis	4	2		3		3		6
Pulmonary tuberculosis	1		1	1		1		2
Primary focus	2		1	1	1(b)	1		3
Total				18	3	7	1	29
Chronic nasal infection; "scrofulous diathesis"	3	9	2	8		3(c)	3	14
Bronchiectasis		1				1		1
Pulmonary abscess		1				1		1
Bronchitis		2		1	1(d)			2
Asthma		2		1		1		2
Malnutrition and underweight		3		1		2		3
Total	26	22	4	11	1	8	3	23
Undiagnosed		1	2	1		1	1	3
Total	26	23	6	1		1	1	55
Associated diagnosis	5	3	1					9
	21	20	5					46

(a) Not clinically active.
(b) Completely healed primary focus.
(c) Tuberculosis suspected or associated. (Mediastinal tuberculosis.)
(d) No tuberculosis present.

the cases in the tuberculous group showed clinical manifestations or suggested tuberculous disease. In the nontuberculous group the skin reactions with the tuberculin fraction were decidedly superior from the diagnostic standpoint. (Tables 8, 9 and 10.)

SUPPLEMENTARY SERIES

In a group of 46 patients ranging from $2\frac{1}{2}$ to 13 years of age, the comparative intracutaneous skin tests made with O.T and T.E. resulted similarly to those described in the larger series. This additional group has been added primarily to record the results of some tests in which O.T. and T.E. were simultaneously used for retesting patients who had been previously tested with O.T. alone. For this material the writers are indebted to Dr. Chesley Bush, Superintendent and Medical Director of the Arroyo Sanatorium, Livermore, California, under whose direction the tests were made by his associates, Drs. Ianne and Brier. As the subjoined table shows, the reactions with T.E. compared with O.T. were better correlated in the presence of clinical findings suggested by or associated with tuberculosis. (Table 11.)

Of particular interest was the group of 12 patients who were retested with O.T. and T.E. 1 to $11\frac{1}{2}$ months after the first test with O.T., seven after 1 to 3 months, four after 6 to $7\frac{1}{2}$ months, and one after $11\frac{1}{2}$ months. There were 6 patients who had reacted negatively to O.T, and the others had shown slightly to moderately positive tests. The T.E. uniformly resulted in more marked reactions, that were usually four, five and even ten times as great in area and intensity compared with the simultaneously retested O.T. The amount of tuberculin used was 0.1 mgm. in all cases.

It was concluded that a tuberculin test with T.E. should be considered positive if it measured more than 5 x 5 mm. and the control test was negative, even when the reaction had faded completely 48–72 hours later. A test that did not fade would be interpreted as indicating more or less allergy. (Table 12.)

The question of the possible effect exerted by a previous injection of tuberculin upon the development of a stronger reaction to a subsequent injection (21) did not affect these results, as the comparative tests indicate. Sufficient time had elapsed between retesting to preclude the enhancement of reaction which might have occurred when O.T was used. For, with reference to the T.E., this factor was of no moment because sensitization to products in the culture media could not have taken place. It is important that we distinguish between specific and nonspecific reactions following repeated injections of substances containing tuberculin along with protein from culture media. This criticism cannot be applied to the use of "synthetic" nonprotein media, in which the products of the tubercle bacillus are elaborated without reference to foreign

TABLE 12

FIRST TEST WITH OLD TUBERCULIN	DIAGNOSIS	RETEST WITH OLD TUBERCULIN*	RETEST WITH TUBERCULIN FRACTION (T.E.)
Patient J. S., noncontact, age 12, 10–5–27 negative	Hilum and peribronchial tuberculosis (active)	11–2–27: 19 x 15 mm.; 48 hours, 5 x 5 mm., fading; 72 hours, negative. 1 month.*	11–2–27: 35 x 20 mm.; 48 hours, 12 x 18 mm. 24-hour control, negative
Patient D. C., contact, age 7, 7-27-27 negative	Hilum and peribronchial tuberculosis	11–2–27: 7 x 10 mm. with induration; 48 hours, 5 x 6 mm., faded; 72 hours, negative 3 months	11-2-27: 31 x 19 mm.; 48 hours, 8 x 8 mm., fading; 72 hours, negative. 48-hour controls negative
Patient V. G., contact, age 7, 4–27–27 negative	Hilum and peribronchial tuberculosis	11–2–27: 20 x 19 mm. with moderate induration; 48 hours, 5 x 7 mm.; 72 hours, 6 x 6 mm. 6½ months	11–2–27: 22 x 27 mm. with marked induration; 48 hours, 8 x 12 mm.; 72 hours, 7 x 8 mm. 24-hour controls, 5 x 5 mm.
Patient L. V., noncontact, age 10, 10–12–27 negative	Asthma (?)	11–2–27: 8 x 10 mm.; 48 hours, 5 x 6 mm., fading; 72 hours, 5 x 5 mm., pale 3 weeks	11–2–27: 10 x 10 mm.; 48 hours, 7 x 8 mm. with definite marked induration; 72 hours, 6 x 7 mm. 24-hour controls negative
Patient L. F., contact, age 12, 5–5–27 negative	Hilum and peribronchial tuberculosis	11–2–27: 6 x 7 mm.; 48 and 72 hours, negative 6 months	11–2–27: 23 x 20 mm. with profound induration; 48 hours, 6 x 8 mm.; 72 hours, 6 x 8 mm., pale. 24-hour controls, negative
Patient H. S. H., noncontact, age 11, 7–27–27 negative	Chronic nasal infection; urticaria. ("Scrofulous diathesis")	11–2–27: 13 x 16 mm.; 48 hours and 72 hours, negative 3 months	11–2–27: 25 x 20 mm. with definite induration; 48 hours, negative; 72 hours, negative. 24-hour controls, 5 x 5 mm.

Patient D. T., contact, age 9, 3-16-27, 4 x 4 mm.	Hilum and peribronchial tuberculosis	11-2-27: 6 x 6 mm.; 48 hours, 5 x 5 mm., pale; 72 hours negative 7½ months	11-2-27: 30 x 18 mm.; 48 hours, 8 x 8 mm.; 72 hours, 4 x 6 mm. with slight induration. 24-hour controls negative
Patient L. S., noncontact, age 12, 3-30-27, 12 x 14 mm.		11-2-27: 3 x 3 mm.; 48 hours and 72 hours, negative 7 months	11-2-27: 20 x 15 mm.; 48 and 72 hours, negative. 24-hour controls negative
Patient L. P., contact, age 7, 8-17-27, 8 x 9 mm., pale	Hilum and peribronchial tuberculosis	11-2-27: 17 x 15 mm.; 48 hours, 5 x 4 mm., fading; 72 hours, negative 2½ months	11-2-27: 22 x 19 mm. with marked induration; 48 hours, 7 x 9 mm.; 72 hours, 7 x 8 mm. 24-hour controls negative
Patient T. T., noncontact, age 13, 9-7-27, 7 x 11 mm., pale	Chronic nasal infection. ("Scrofulous diathesis")	11-2-27: 16 x 20 mm. with marked induration; 48 hours, 6 x 6 mm., fading; 72 hours, 6 x 7 mm., pale 2 months	11-2-27: 38 x 20 mm.; 48 hours, 6 x 8 mm. with marked induration; 72 hours, 6 x 8 mm., pale. 24-hour controls negative
Patient P. S., noncontact, age 9, 12-20-26, 8 x 9 mm.	Chronic nasal infection. ("Scrofulous diathesis")	11-2-27: 3 x 2 mm.; 48 and 72 hours, negative 11½ months	11-2-27: 37 x 20 mm. with marked induration; 48 hours, 8 x 8 mm. with induration; 72 hours, 10 x 10 mm. 24-hour controls negative
Patient J. I., noncontact, age 9, 9-7-27, 5 x 5 mm.	Chronic nasal infection. ("Scrofulous diathesis")	11-2-27: 4 x 6 mm.; 48 hours, 4 x 5 mm.; 72 hours, 4 x 6 mm. 2 months	11-2-27: 20 x 20 mm. with marked induration; 48 hours, 10 x 10 mm. with deep induration; 72 hours 9 x 8 mm. 24-hour controls negative

* Time elapsed between tests.

proteins. In this instance sensitization that might develop from repeated injections of T.E. would indicate a specific response to the bacillary substances. Only in this sense, therefore, could it be correctly stated that sensitization to tuberculin might occur.

DISCUSSION AND SUMMARY

In the evaluation of comparative skin reactions for tuberculosis, two points might be considered; first, the diagnostic value in relation to tuberculous infection, and, second, the relation to clinical disease. The supposition might be made that a strong test is to be associated with clinical activity and the weak or negative one be not so associated. The diagnostic superiority of a test would appear to rest in its ability to give a stronger reaction when only clinical disease existed to the exclusion of any cases with old, healed foci. As a corollary to this point, when a strong reaction with O.T. might lead one to believe that a weak reaction is valueless, the fractional tuberculin in such a case might give better information because the correlated results tend to show that nonclinical tuberculosis may be differentiated from tuberculous disease. In our experience the fractional tuberculin has never failed to give unequivocally positive results in definite tuberculous disease.

Three hundred and forty-six tuberculous and nontuberculous patients, ranging in age from seven months to sixteen years, have been studied with a view to comparing tuberculin reactions with specially prepared fractions of tuberculin. The cases have been divided into various groups to test more rigorously the diagnostic value of the tuberculin fractions. To this end borderline groups, presenting unusual difficulty in diagnosis, were selected. Stress was laid particularly upon healed infections. The chief differences in the reactions in those cases pointed to lesser reactivity on the part of the tuberculin fractions in latent conditions in which O.T. gave moderate or marked reactions. The results indicate also that a diagnosis of healed tuberculous cervical adenitis or of a healed primary focus cannot be made with certainty in the absence of a definitely marked positive reaction to O.T.

Tuberculin fractions did not give negative tests when O.T. was positive in patients having symptoms that might be considered as those of tuberculous activity. In all the cases in which the tuberculin fraction gave reactions equal to those with O.T., when it showed medium or strong tests, or in cases in which the fraction gave medium to strong and O.T. at the same time gave weak to doubtful results, symptoms and signs

were present in the history that might have been attributable to tuberculous activity.

In a clinically normal group, equally divided between contact and noncontact patients with tuberculous infection but without any active process, the marked O.T. reactions gave information that was not consistent with the clinical picture. In these instances, the lesser reactivity or negative results with the tuberculin fraction might be more significant, particularly when negative results give more information.

In a paper that is now being prepared there will be presented the detailed analysis and evaluation of the symptoms, signs and clinical observations made in these same groups of patients with special reference to diagnoses and the skin reactions.

CONCLUSION

From detailed analyses of the different tuberculous and nontuberculous groups presented, it can be concluded that the tuberculin preparation, a fraction described as T.E. (alcohol- and ether-insoluble), gives better results in our hands than ordinary O.T. and is more selective as a clinical test. The preparation and use of this tuberculin fraction are described and discussed.

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BLOOD-SERUM CALCIUM IN THE NEGRO[1]

A Laboratory Study

C. LYDON HARRELL

For several years Dr. Grandy and I have noticed in the tuberculosis clinic at Norfolk, Virginia, that many negroes with tuberculosis "went down hill" very rapidly, after they once became sick enough to consult a physician. Some seem to have very little resistance to the disease, dying within six to twelve months after tuberculosis was recognized. At the same time white people under the same conditions and treatment would live from three to five years or longer.

About a year ago while reviewing some of the cases, it was suggested that a low blood-calcium might have some bearing on the rapid development of the disease. In order to determine this, I volunteered to run a series of blood-calciums in our laboratory. I was unable to find anything in the literature relating to blood-calcium in the negro. We then thought it best to run a series on apparently healthy individuals, in order to establish a normal for the negro.

In group 1 there were 44 cases, so far as I was able to determine by physical examination, that had no chest pathological changes. The average calcium in this group was 10.93 gm. per 100 cc. of blood. This is 0.43 gm. higher than the normal blood-calcium as given for the white individual, which is 10.50 gm. My explanation of this is that the negro is exposed to the sun-rays more than the white man, and that he eats rather freely of three forms of foods that are very rich in calcium, namely, cheese, cabbage and turnips; that is, when he is well and at work. In the first group there were 7 cases that gave a 4-plus Wassermann. Their average calcium was 10.37 gm., which was 0.56 gm. lower than the normal or average for this whole group.

In the second group which were diagnosed as either suspicious or having definite tuberculosis there were 41 cases. The blood-calcium in this group averaged 9.8 gm., which was 1.13 gm. lower than my established normal. In this group there were 7 that gave a 4-plus Wassermann; their average calcium was 9.6 gm., which was still a little lower

[1] Read before the Norfolk County Medical Society, Norfolk, Virginia, October 12, 1928.

than the average for the entire group, or those having only chest involvement. After sifting this group down, and eliminating the suspicious cases, there were 23 cases diagnosed as having positive pulmonary tuberculosis. The average calcium for this positive group of 23 cases was 9.2 gm., or 1.73 gm. below the established normal. Six of these cases died while their investigation was being made. Their average calcium was 9.1 gm.

DISCUSSION

We learn from the above figures that hypocalcaemia is the effect of disease. As the disease progresses the calcium content of the blood often drops accordingly. This may probably help to explain the lowered resistance we often find in tuberculosis patients, especially negroes.

In order for fibrosis or healing to take place there must be an abundance of calcium, and if this is not forthcoming the opposite is the result. McLester, in his book on dietetics, quotes the work of Nelson and Williams, showing that healthy men on a restricted diet excreted from 0.68 to 1.02 gm. of calcium a day. To allow a sufficient margin of safety, we should assume that the average man, in order to preserve equilibrium, must have an intake of at least 0.75 gm. of calcium daily. I should think that a sick man would require even more than this.

Now, what happens with a negro who develops tuberculosis is this: First, his appetite fails as the result of disease, and he does not eat enough. Second, his income is cut off and he is not able to buy the kind or quantity of food he requires. He shuts himself up in a close, dark room, depriving himself of the essentials in successfully handling any tuberculosis case, namely, rest, nourishing food, fresh air and sunshine. He gets his rest, but at the expense of the other three restorative factors; consequently the disease develops very rapidly.

There are a few symptoms that often develop in these cases as a result of the calcium imbalance that would be well for us to bear in mind, such as acute coryza and other nose and throat complications, asthma, and certain types of spasmodic cough. It behooves us who handle these patients to see that they maintain a proper calcium balance by getting plenty of sunshine, and partaking of food rich in assimilable calcium; as, for instance, milk, cheese, dried beans, beets, cabbage, carrots, turnips, oranges and almonds. You will notice that most of these are within the reach of the average man's purse; only three,—milk, oranges and almonds,— may be considered expensive.

I fear that fats and carbohydrates are being pushed too far. A gain in weight is not the prime object in the cure of tuberculosis, though this is desirable. In order for healing to take place, either by resolution or by fibrosis, a proper balance of minerals and vitamines must be obtained.

The above material was furnished by the tuberculosis clinic under the supervision of Dr. Chas. R. Grandy. All of the physical examinations were done by the author, and the laboratory work by Miss Jeanette Erdol.

Discussion: Dr. Grandy: As Dr. Harrell has said, we have been vainly searching for any clue which might explain the lack of resistance to tuberculosis on the part of the negro.

We have noted both clinically and in X-ray pictures that the negro did not apparently show the same ability as the white man to form scar-tissue or calcification in resisting tuberculosis. So I suggested that we might find a deficiency of blood-calcium in the negro.

While Dr. Harrell's study does not show this to be true in the healthy negro, it does show that the blood-calcium falls more rapidly in a case of tuberculosis in a negro than in a white man.

It thus at least may be taken as an index of his susceptibility, though probably a result rather than a cause of this.

This piece of work seems to be very well worth while, and I hope it will stimulate others to try to shed more light on this unsolved problem.

STUDIES ON PULMONARY ACOUSTICS

I. AN APPARATUS FOR RECORDING RESPIRATORY SOUNDS[1]

P. F. METILDI AND R. S. LYMAN

With the technical assistance of

Y. W. LEE[2] AND F. W. BISHOP[3]

In order to record respiratory sounds graphically on an instrument of sufficiently high inherent frequency, it was necessary to amplify them considerably. This was accomplished by using an electrical stethoscope constructed by The Western Electric Company of New York (1). It operates on radio principles, and consists of a contact electromagnetic transmitter, various transformers, a three-stage amplifying system and electrical filters. A condenser transmitter is also supplied.

The contact transmitter "picks up" the vibrations of the chest-wall produced by the respiratory sounds, and transforms them into electrical energy, which is amplified by three three-electrode vacuum tubes after having passed through suitable transformers. The amplification of the sounds to be studied can be controlled at will, and in this apparatus it has an arbitrary scale from 0 to 22. It is designated as *Vol. Contr.* in the appended charts. The amplified vibrations may or may not be passed through filters, as desired, and are then recorded on an oscillograph.

The electrical filters in the stethoscope are a combination of condensers and coils (2), which cut off or greatly diminish oscillating currents of frequencies above or below a certain range. Our apparatus is supplied with the following:

H. P. (High Pass) 50, which allows currents of frequencies above 50 cycles per second to come through, and suppresses or greatly diminishes those below that rate
H. P. 130
H. P. 250

[1] From the Department of Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, New York.
[2] Massachusetts Institute of Technology.
[3] University of Rochester.

L. P. (Low Pass) 130 which allows currents of frequencies below 130 to come through, and suppresses or greatly diminishes those above that rate
L. P. 400
L. P. 600
L. P. 1100

The oscillograph used is *Type EM Form C*, manufactured by The General Electric Company of Schenectady, New York (3). It consists of a galvanometer with three vibrators and a suitable optical system for directing beams of light from an arc-lamp to the respective mirrors on the vibrating elements and from there to a revolving film. Each vibrator is a single loop of flat wire, with a small mirror cemented across the two sides of the loop, with its face in a plane parallel to the magnetic lines of force.

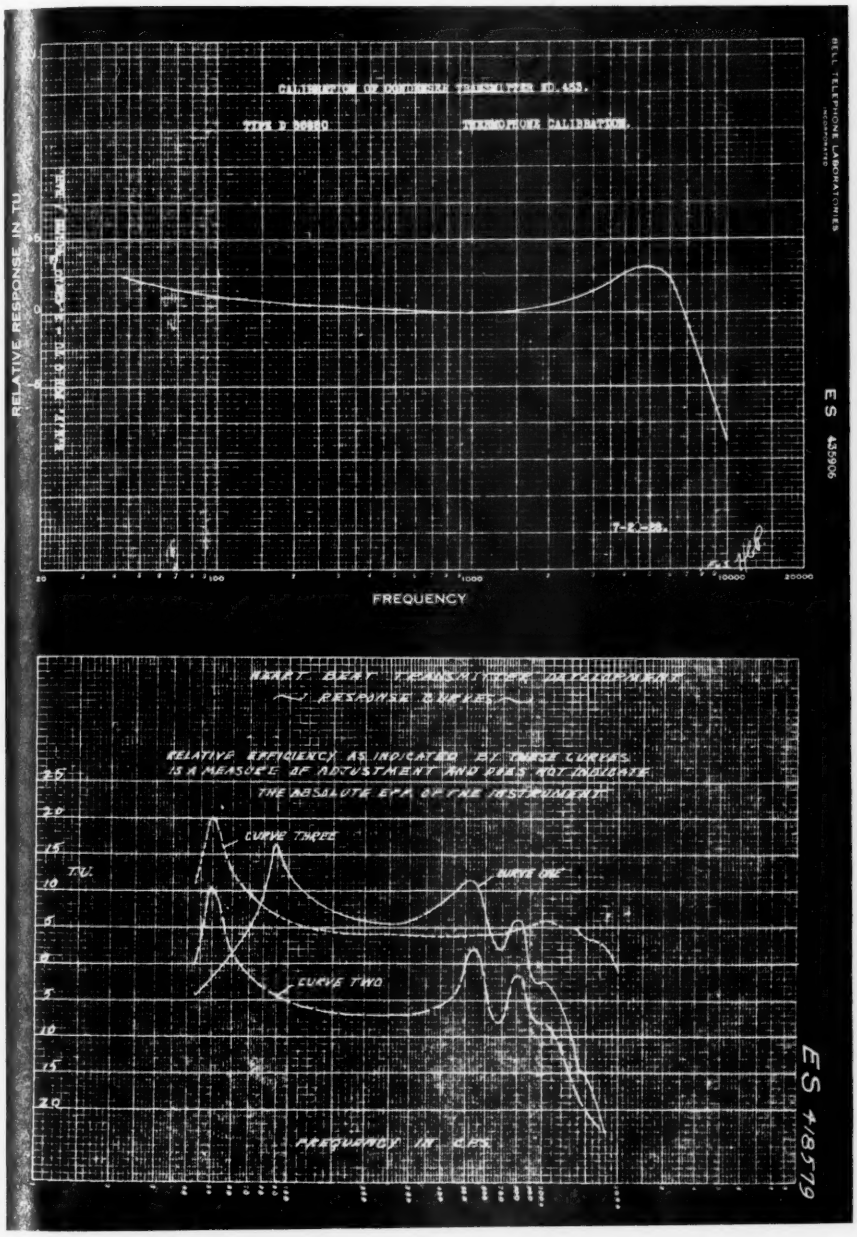
CHART 1. CALIBRATION OF TRANSMITTERS

Above: Condenser Transmitter: Smooth curve, which is nearly flat between 40 and 4000 vibrations per second, indicating no appreciable distortion throughout the range of chest sounds.

Below: Electromagnetic Transmitters: Characteristics of three forms of transmitter operating on same principle. Curve 3 applies to special instrument with light wooden vibrating element in a heavy stationary brass casing; presents a peak at 50 vib. sec., but a relatively flat line between 80 and 1500 vib. sec., allowing no essential distortion through that latter range. Curve 1 represents the transmitter provided on the market as part of the electrical stethoscope; has peaks at about 90 and 560 vib. sec., giving some exaggeration in loudness of sounds at equivalent pitches; above 800 vib. sec. the sensitiveness falls off rapidly. Curve 2 not in use with the apparatus at hand.

In recording sound a "high sensitivity" vibrator is used. It requires 0.0015 amp. per millimetre deflection when its tension is 4 oz. and has an inherent vibration frequency of 3000 complete oscillations per second. This last property is its chief advantage, since with it one can record sounds up to 3000 vibrations per second, which is impossible with the usual string galvanometer.

Since the impedance of the circuit in the stethoscope is about 6000 ohms and the resistance of the vibrating string in the oscillograph is 1.5 ohms (when the gold-leaf fuse is eliminated), it was found necessary to add a "step-down" transformer between the stethoscope and the oscillograph, which increased the sensitivity of the apparatus considerably. A transformer with a ratio 8000:2, previously designed by C. F. Sacia of the Bell Telephone Laboratories of New York, served the purpose sufficiently well.


RELATIVE RESPONSE IN TU
FREQUENCY
BELL TELEPHONE LABORATORIES
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7-2-28.
CURVE THREE
CURVE ONE
CURVE TWO
TU.
FREQUENCY IN CPS.
ES 418579

CHART 1

One of the vibrators of the oscillograph is used for a tuning fork (100 vibrations per sec.) and the middle vibrator for sound. In place of the third, a Frank Capsule attached to a pneumograph is substituted, in order to record the phase of respiratory movements when dealing with breath-sounds.

The stethoscope and the source of sound to be recorded are placed in a small room, the walls of which are lined with Johns-Manville felt and insulite. The room is surrounded by a grounded copper screen, in order to eliminate induction from alternating room-currents, which, when present, are amplified by the stethoscope, and thus interfere considerably. Between the copper screen and the insulite is a 2-inch layer of coarsely ground cork. The floor of the room is of the "Stevens Floating" type, which diminishes the conduction of vibrations from the building. It is covered with a 1-inch layer of solid cork, and on top of it rests a layer of linoleum. Inside the room one finds a reduction but not total elimination of extraneous noises and vibrations.

Calibration curves of the electromagnetic transmitter, stethoscope and filters, showing their respective characteristics, are published in the *Bulletin* of The Western Electric Company. However, it was considered advisable to calibrate the complete apparatus, including the oscillograph, just as used in the following experiments, in order to obtain the exact characteristics of the system as a whole. The contact transmitter could not be included in this method of calibration and for that reason its characteristics are shown separately in chart 1. The condenser transmitter is preferred for some experiments, and calibrations of this instrument are also added on chart 1.

The data for the curves shown on charts 2 and 3 were obtained by introducing into the circuit varying vibrations of a sinusoidal type of known frequencies, the amplitudes of which were measured accurately with a thermocouple and a galvanometer. These vibrations were produced by a General Electric oscillator procured from the WHAM Broadcasting Station of The Stromberg-Carlson Company of Rochester, N. Y. The waves introduced were first photographed and found to be pure sinusoidal waves. The deflections of the vibrating strings in the oscillograph were recorded on a photographic film. In that way the amplitudes of the vibrations at different frequencies were determined and then plotted against each other as shown on the appended charts.

Chart 2 shows the uniformity of results obtained by varying the amplification (*Vol. Contr.*) and increasing the input, or loudness of the sound.

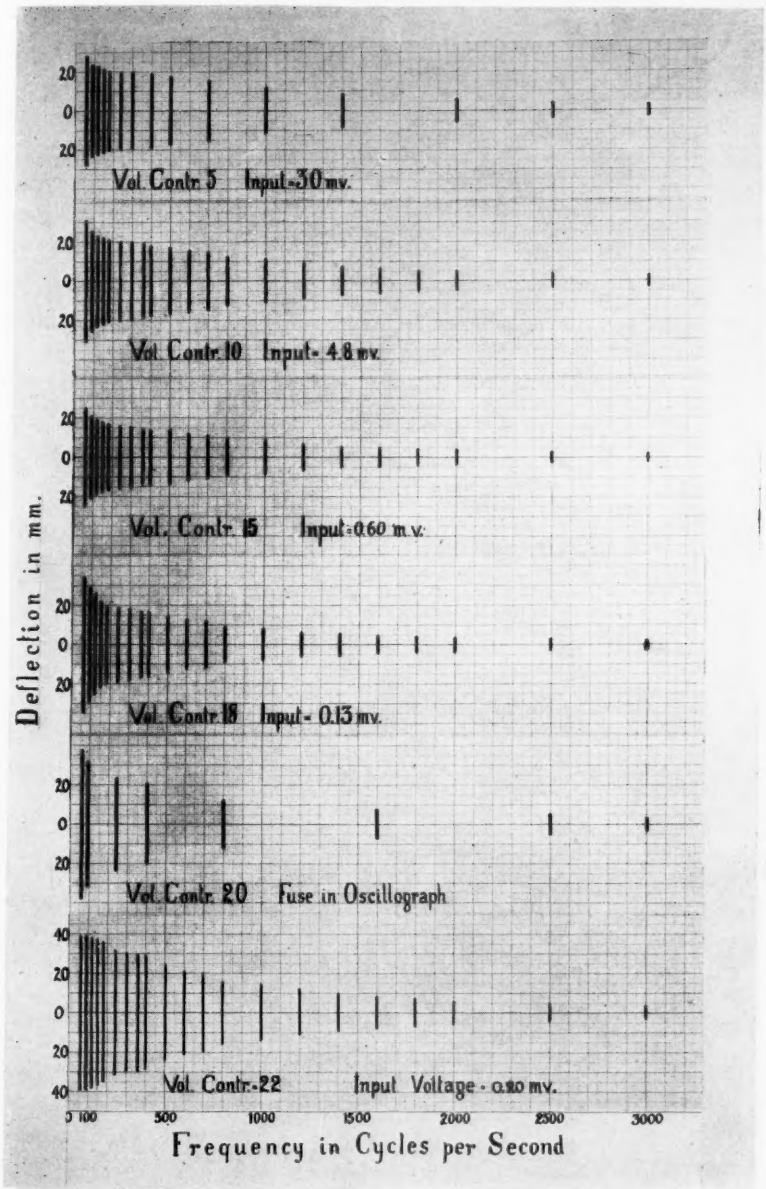
Deflection in mm.
20
0
20
Vol. Contr. 5 Input-30 mv.
Vol. Contr. 10 Input- 4.8 mv.
Vol. Contr. 15 Input-0.60 m.v.
Vol. Contr. 18 Input- 0.13 mv.
Vol. Contr. 20 Fuse in Oscillograph
40
Vol. Contr.-22 Input Voltage - 0.10 mv.
0 100 500 1000 1500 2000 2500 3000
Frequency in Cycles per Second

CHART 2. CALIBRATION OF ELECTRICAL STETHOSCOPE, OSCILLOGRAPH AND CONNECTIONS AS A UNIT, NOT INCLUDING TRANSMITTERS

Deflection of vibrating string of oscillograph on introducing into the system vibrations of known frequencies. Shows similarity of results at different amplifications in the electrical stethoscope. As the wave-frequency (pitch of sounds) gets higher, there is a progressive decrease in extent of deflection of the string (loudness).

In the case of each set of observations the input was adjusted roughly, so as to demonstrate similarity in the general shape of all curves. That input was kept constant for the specific amplification which is shown on

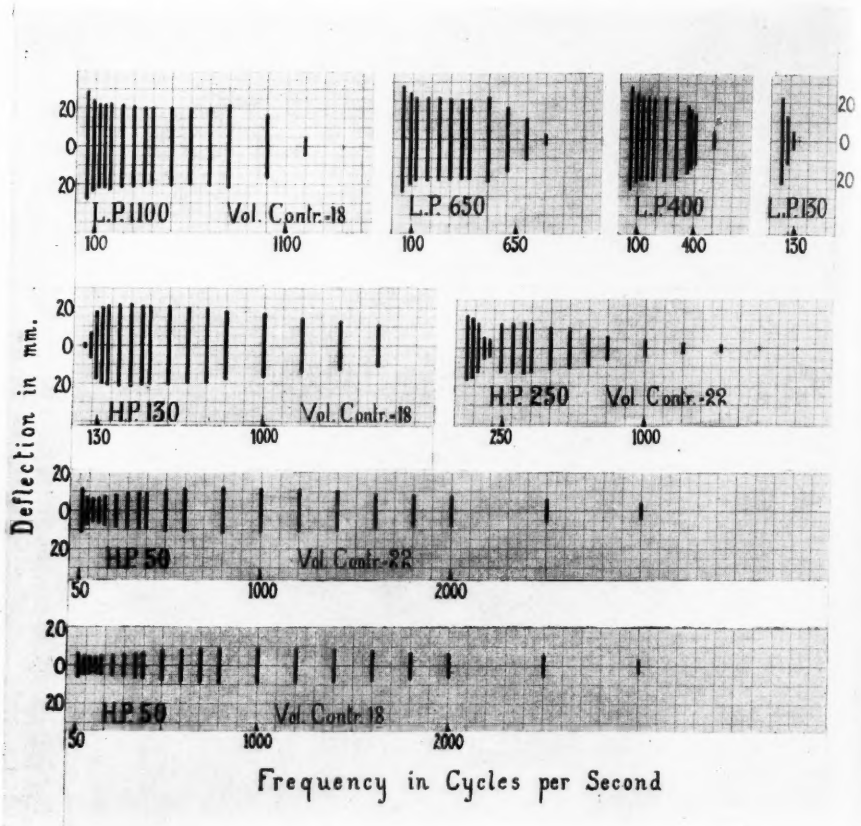

CHART 3. CALIBRATION OF FILTERS IN THE SAME SYSTEM AS APPEARS ON CHART 2

Theoretical "cut-off" points for each filter are indicated by numbers at the bottom of each curve. Actual wave-frequencies which are passed by each filter are recorded as black bars which show the deflection of the string in the oscillograph in millimetres on the ground-glass screen. The amplification (*Vol. Contr.*) is constant throughout each curve.

each separate curve, although the input on one curve was not necessarily identical with that on all others.

It will be seen from these curves that the amplitude of deflection decreases as the frequency increases. When one considers the characteristics of the contact transmitter, one can see that, in the lower range, the

latter offsets the tendency of the rest of the system to accentuate frequencies below 100 vibrations per sec. However, such a fortunate combination does not occur in the range above 2000 vibrations per sec.

Chart 3 shows the effect of the filters. The amplification in the case of all filters was the same (*Vol. Contr. 18*) unless otherwise specified on the individual curves. It is apparent here that the filters have not very sharp cut-off frequency characteristics, but, even so, their use is justified if one considers their exact properties in evaluating their effects.

SUMMARY

1. An apparatus is described in which a contact transmitter responds to the mechanical vibrations that are heard as sound and transforms them into waves of electrical energy. These waves are amplified in an electric stethoscope and are carried to an oscillograph, where corresponding deflections of a vibrating string are optically magnified and photographed on a moving film.

2. Calibration curves of the complete system are presented.

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STUDIES ON PULMONARY ACOUSTICS

II. THE TRANSMISSION OF TRACHEAL SOUNDS THROUGH FRESHLY EXENTERATED SHEEP'S LUNGS[1]

R. R. HANNON AND R. S. LYMAN

With the technical assistance of

Y. W. LEE[2]

An old experiment on the transmission of tracheal respiratory sounds through exenterated lungs was repeated with means of recording the results quantitatively. Lungs from healthy sheep were laid across the throat of a normal adult male subject. The effect on the passage of tracheal breath-sounds through the sheep's lungs was then registered.

In the past, auscultation of sounds produced under similar circumstances has led to several divergent statements. One view, which was backed, for example, by C. Gerhardt (1) and also by Martini (2), admitted a change in the tracheal sounds, which then acquired partial similarity to the vesicular quality,—that is, soft, relatively low-pitched, "murmuring." Sahli (3) flatly denied that tracheal sounds could be called "vesicular" after their transit through lung-preparations. He "has never heard anything but a weakened blowing tracheal murmur." His extreme stand is contrasted with that which he attributes to Baas, and which is supported by Penzold (4), namely, tracheal respiration becomes definitely "vesicular" in all respects in passing through normal lung-tissue. All seem to agree that inflation of the lungs leads to some modification of transmitted tracheal sounds. It rested with Martini to offer most convincingly the proposition that with air-containing lungs the sound is not much different from that obtained through the chest-wall from healthy lungs, and that it is chiefly the high-pitched sounds which are lost.

This present report now affords graphic records of respiratory sounds taken directly over the trachea, of tracheal sounds transmitted through a constant thickness of sheep's lung-tissue expanded at different pressures,

[1] From the Department of Medicine, University of Rochester, School of Medicine and Dentistry, Rochester, New York.

[2] Massachusetts Institute of Technology.

and of vesicular breath-sounds obtained at the right base of the chest of the same subject. Their comparison is readily put on a strictly objective basis.

PROCEDURE

The experiments were carried out in a special room which was built so as to reduce extraneous noises. In that room one of us (R. R. H.) served as the subject from whom all respiratory records were taken. The other manipulated the apparatus at hand. This included an electromagnetic transmitter and the electrical stethoscope. Of the electric filters which are provided with the stethoscope, the low pass 650, low pass 400, and low pass 130 were used in these experiments. From the electrical stethoscope connections were made with an oscillograph, which was operated by a third person in an adjoining room. The apparatus is further described in another report (5).

Sheep's lungs were procured at a nearby slaughter-house. The time was noted when the throat of a sheep was cut. On removal of its lungs and heart, they were rinsed off with warm normal saline solution and were wrapped in warm towels moistened with the saline solution. On arrival at the hospital the heart was dissected away and a cannula was tied into the trachea. Again the lungs were wrapped in towels moistened with warm normal salt solution and were taken into the "sound-proof" room. There the cannula in the trachea was connected by a "Y" tube with a water-manometer and an inflating tube. The individual who was subject in these experiments put a pneumograph around his chest and lay down on a cot. Measurements were taken on the sheep's lung with calipers, and the lung was then laid across the neck of the subject so that that level which measured 4.5 cm. in thickness rested with its own weight vertically on the subject's throat. The transmitter was put at the proper place on the lung by the observer, and was then held in that position as steadily as possible by the subject. The pressure of the transmitter against the lung was not measured, but was maintained with the hands as constantly as possible at very nearly its own weight. The observer then listened to the sounds before registration was made on the oscillograph.

The time when the first record was taken in all cases reported here lay between 30 and 40 minutes after the throat of the sheep was cut in the slaughter-house.

The lung was then inflated and deflated once or twice to ensure even filling of the alveoli. A random manometric pressure was taken and the inflating tube was clamped. That left the lung always connected with the manometer. The reading was noted. As long as it stayed constant, the system was considered air-tight. Transmitted sounds were heard and then recorded. The lung was again inflated, deflated, and then maintained under a new pressure. Another measurement was made with the calipers, and the proper region was placed anew on the subject's throat to give a thickness of 4.5 cm. of lung-tissue. Results were photographed as before. That procedure was repeated at different pressures some 4 to 8 times. After each observation the lung was inflated and a satisfactory spontaneous collapse at atmospheric pressure was noted before any further records were taken.

In order to keep the results comparable from day to day with several different sheep's lungs, the amount of amplification in the stethoscope and the tension on the string in the oscillograph were kept constant. The subject tried to breathe quietly at the same rate and depth. The thickness of lung-tissue was always 4.5 cm. The pressure of the transmitter on the lung remained practically constant at just about its own weight. In order to increase the effect of random sampling, the readings were taken at pressures which were not consecutive. The subject was not informed which filters were inserted and was not told the readings on the manometer until afterward.

RESULTS

The results of these experiments are summarized on charts 1 to 4. Each chart presents a series of observations obtained at the same sitting, although the order in which the records were taken did not follow the successive changes of pressure which appear in sequence on the charts.

The line which appears uppermost on each reproduction shows the phase of respiration. Since the pneumograph was not put on at the same tension on consecutive days and did not always stay at the same place on the trunk, the slope of that line is no guide to the relative depth of respiration. Further, there is a slight delay between the action of the pneumograph and the thoracic air-currents or, in other words, the movements of the chest wall are slightly in advance of the air-stream. The middle curve represents the sounds. At the bottom, time is indicated at intervals of 1/100th of a second.

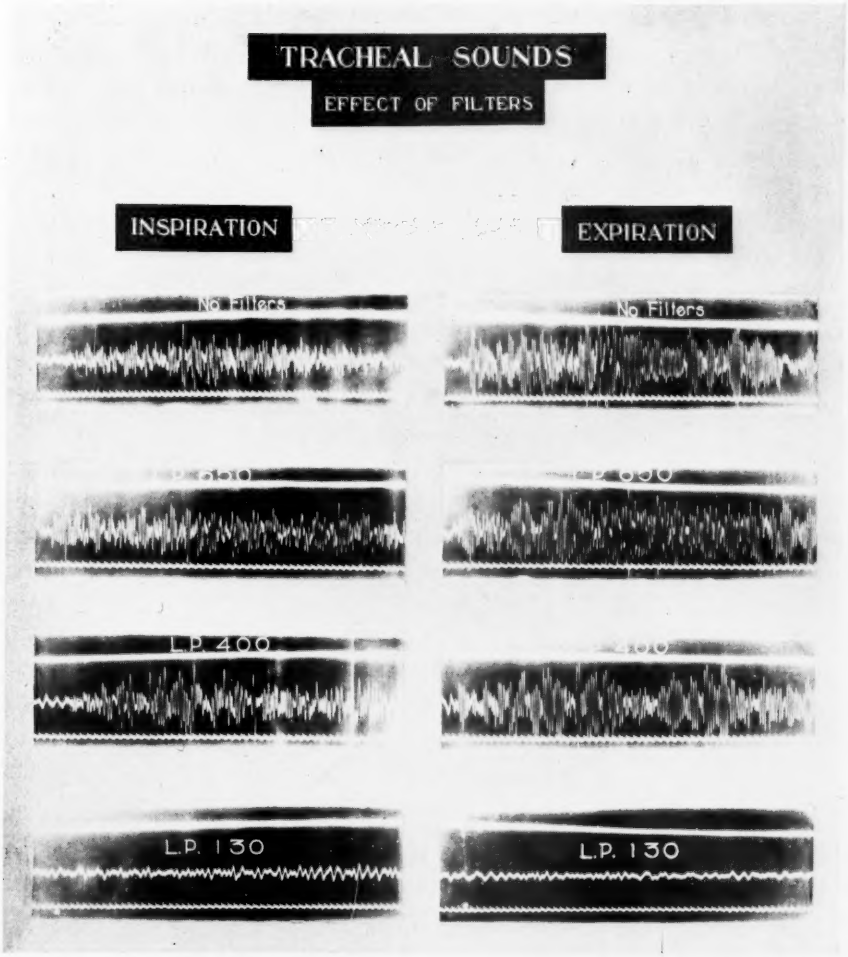

CHART 1. TRACHEAL SOUNDS, TAKEN WITH TRANSMITTER LYING DIRECTLY ON THE NECK

Upper pair of curves: No filters. In expiration deflections are wider (sounds louder) and continue through a longer duration than in inspiration. Frequency of oscillations (pitch) about the same in both phases.

Second pair: Wave-frequencies below about 650 vibrations per second appear. Characteristics essentially the same as with no filters.

Third pair: Wave-frequencies below about 400 vibrations per second appear. Same general appearance as above.

Bottom pair: Wave-frequencies below about 130 vibrations per second appear. Marked decrease in amplitude of oscillations (sounds much softer). Inspiratory breath-sounds show definitely wider deflections than expiratory, the three large waves which are starred at the beginning of expiration being transmitted from the arterial pulse of the neck (see text). Inspiration soft but definitely audible on auscultation.

Inspiration and expiration are shown here on short prints taken from the long films, in each case starting with the quiet period preceding the respiratory sound but not always reproducing each period throughout to its completion. Each expiratory phase which appears on the charts directly followed the inspiratory phase, or *vice versa*. That depended on the position on which they fell by chance on the original films, which were long enough to include a little more than one whole respiratory cycle.

Tracheal respiration corresponds audibly and graphically (chart 1). Without filters, expiration shows definitely greater amplitude of vibrations (louder) and is longer in total duration than inspiration. The frequency of waves (pitch) is not very different in the two phases, but in both it is far higher than in vesicular breathing. When a count is made on the records without filters, the frequency during inspiration varies from about 166 to 2000 complete oscillations, while it ranges between about 180 and 2000 vibrations per second in expiration. The peak in each phase lies between 286 and 400 vibrations per second on distribution charts. The low frequencies are hard to determine on account of the overwhelming preponderance of waves above about 300 per second. That the majority of wave-frequencies are below 650 per second is also shown on the films by the absence of appreciable change on introducing the low pass 650 filter. In fact, the pattern is not greatly altered by adding the low pass 400 filter. When any of these filters is inserted, there is a slight decrease in amplitude of the waves due to some absorption of electrical energy in its passage through the filter. A pronounced difference in the tracheal sounds is seen when the low pass 130 filter is used. Distinct vibrations which were previously masked by the more rapid deflections now appear, although they are small in amplitude. These results fall in with previous reports from several other sources. Fahr (6), for example, "found tracheal breath sounds composed of vibrations between 400 and 660 vibrations a second. A not inconsiderable portion of the sound energy consisted in vibrations between 660 and 1000 a second. A small amount of the sound energy consisted of vibrations between 120 and 400 a second." The records shown here bring out, however, one additional point which seems significant. It is clear that without filters expiration is markedly louder than inspiration. It is equally certain, that, with the low pass 130 filter, inspiration produced wider deflections of the vibrating string than did

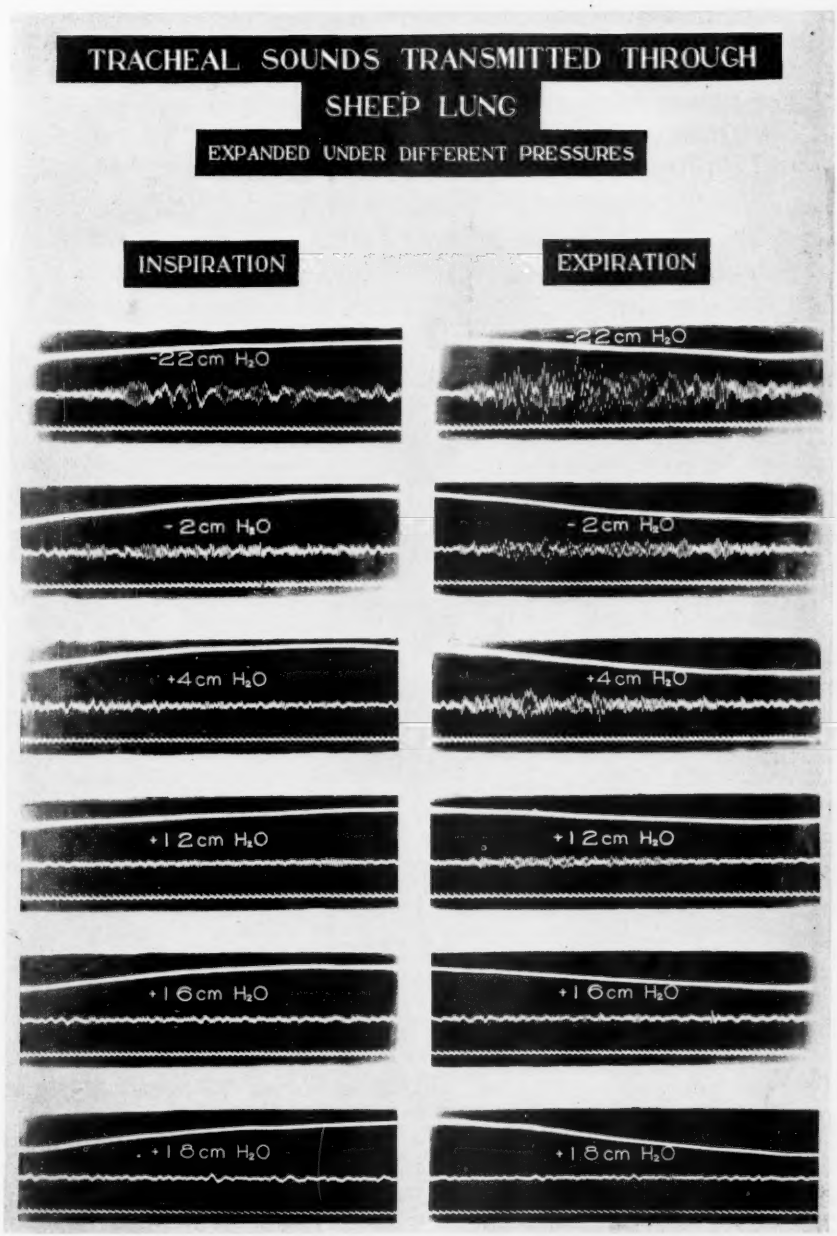

CHART 2. TRACHEAL SOUNDS TRANSMITTED THROUGH A CONSTANT THICKNESS OF SHEEP'S LUNG EXPANDED UNDER DIFFERENT PRESSURES

No filters used. Amplitude of vibrations (loudness) decreases rapidly as pressure in lungs is increased. Frequency (pitch) also decreases with increasing pressure but less strikingly so. Frequency-counts made under a magnifying glass are given in a table in the text.

expiration in the individual who was the subject in this experiment. That occurred definitely in five different films, which were taken interspersed with records without filters and in an order not known to the person who was breathing. Hence, it seems in the case at hand that the high-pitched tracheal sounds (above about 130 vib. per sec.) predominate in expiration, while the low-pitched tracheal components (below about 130) are more pronounced in inspiration.

The next step was the introduction of sheep's lungs between the trachea and the transmitter. When a collapsed lung was interposed, the tracheal sounds were transmitted with very little change, other than a slight decrease in amplitude. After a lung had once been inflated, a pro-

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CHART 3. EFFECT OF FILTERS ON TRACHEAL SOUNDS TRANSMITTED THROUGH A CONSTANT THICKNESS OF SHEEP'S LUNG EXPANDED UNDER DIFFERENT PRESSURES

1: Collapsed lung under pressure of minus 12 cm. H_2O. Topmost curves, without filters, show the same general characteristics which appear in tracheal breath-sounds on chart 1. In the lower pair only vibrations below about 130 per second are allowed to appear; there is no appreciable deflection of the vibrating string; when listening, nothing could be heard.

2: Lung, previously inflated, under atmospheric pressure. With no filters, appreciable decrease in amplitude, little change in frequency. No significant oscillation of string on introducing low pass 130 filter; no sound on auscultation.

3: Pressure of plus 6 cm. H_2O. Amplitude during expiration somewhat greater than in the record immediately above, by way of exception to general tendency. Pitch practically the same. Again no essential deflection of vibrating string with low pass 130 filter; no sound on auscultation.

4: Pressure of plus 20 cm. H_2O. Minimal amplitude of oscillations without filters; practically total suppression with low pass 130 filter. Waves of higher frequencies suppressed. Transmitted pulsations from arteries in neck of subject, indicated by stars. Breath-sounds inaudible on auscultation with low pass 130 filter in circuit.

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nounced decrease in amplitude of the vibrations appeared, both in inspiration and in expiration. This is shown in the difference between the excursion of the vibrating string in the topmost reproduction (collapsed lung which had not been inflated) and the second one without filters (lung which had been inflated) in charts 2 and 3.

In chart 2 the most striking feature is the progressive diminution in amplitude of the oscillations as the pressure in the lungs is increased. This occurs in both inspiration and expiration. The wave-frequency also decreases. In this chart, counts show the following results:

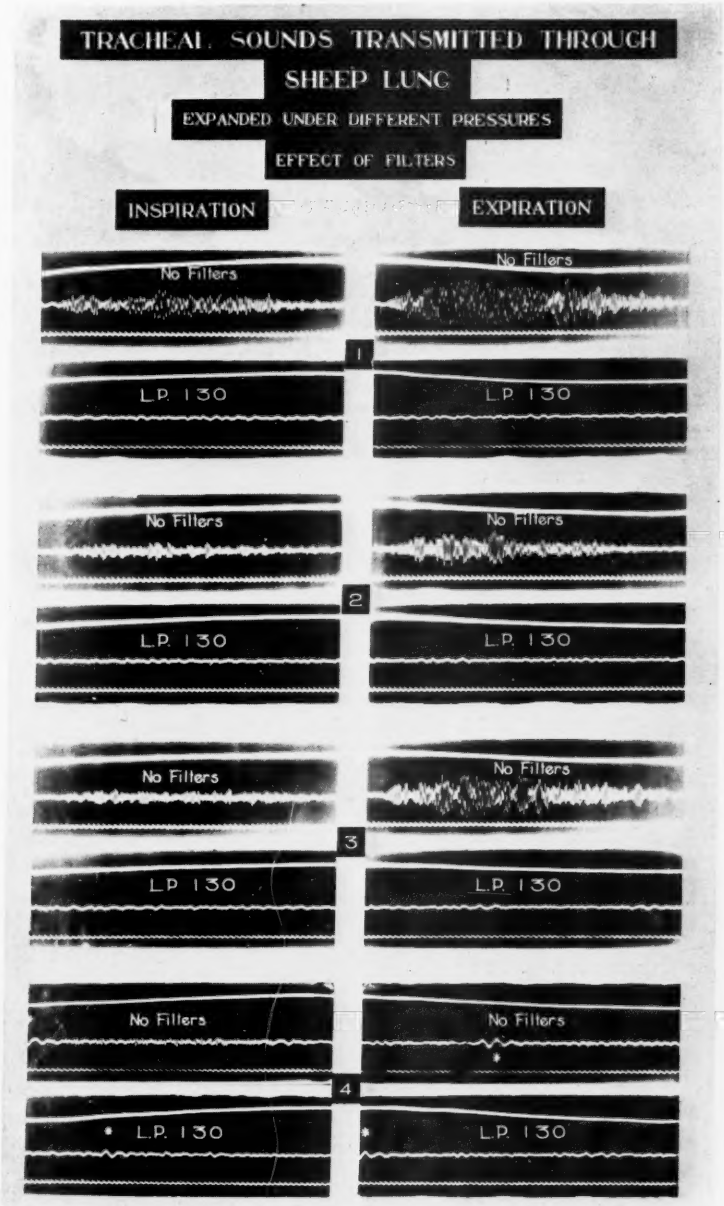
TRACHEAL SOUNDS TRANSMITTED THROUGH
SHEEP LUNG
EXPANDED UNDER DIFFERENT PRESSURES
EFFECT OF FILTERS
INSPIRATION
EXPIRATION
No Filters
No Filters
1
L.P. 130
L.P. 130
No Filters
No Filters
2
L.P. 130
L.P. 130
No Filters
No Filters
3
L.P. 130
L.P. 130
No Filters
No Filters
4
L.P. 130
L.P. 130

CHART 3

Inspiration

Pressure	*Range*	*Peaks on distribution charts*
−22 cm. H_2O	Lower limit uncertain Upper limit 2000	Major: 250 to 400 Minor: 650 to 1000 (pronounced)
−2 cm. H_2O	125 to 1000	Major: 250 to 400 Minor: at 1000 (moderate)
+4 cm. H_2O	125 to 1000	Major: 250 to 400 Minor: at 1000 (moderate)
+12 cm. H_2O	125 to 1000	250 to 400 No minor peak
16 cm. H_2O	125 to 1000 (Few long waves 60 to 100)	Major: 250 to 400 Minor: at 1000 (slight)
18 cm. H_2O	125 to 1000 (Few long waves 40 to 70)	350 to 400 No minor peak

Expiration

Pressure	*Range*	*Peaks on distribution charts*
−22 cm. H_2O	200 to 2000	Major: 250 to 400 Minor: 650 to 2000 (pronounced)
−2 cm. H_2O	150 to 1500	Major: 250 to 400 Minor: at 1000 (moderate)
+4 cm. H_2O	125 to 1500	Major: 250 to 400 Minor: at 1000 (moderate)
+12 cm. H_2O	200 to 1000	Major: 250 to 400 Minor: at 1000 (moderate)
+16 cm. H_2O	250 to 1000 (A few long waves 60 to 100)	Major: 250 to 400 Minor: at 1000 (slight)
+18 cm. H_2O	250 to 1000 (Occasional long waves 40 to 70)	Major: 350 to 400 No minor peak

In chart 3 four sets of records appear. The first represents collapsed lung (not previously inflated) at a pressure of minus 12 cm. of water. The second is taken from the lung (after being inflated) at atmospheric pressure, the third at plus 6 cm. of water, and the fourth at plus 20 cm. of water. Those records which are labelled "No filters" show the same features which appear on chart 2. In chart 3, however, filters are used in addition. The low pass 650 and 400 filters have been seen to produce no great change in the tracheal sounds which are taken directly over the throat (chart 1). They were also tried in this experiment, which is summarized on chart 3, in the case of the collapsed lung at minus 12 cm. of water, *1*, and in that of the lung inflated at plus 6 cm. of water, *3*. No significant differences could be noted on the films before and after their introduction. Hence they are not included on this chart. On the other hand, when the low pass 130 filter was inserted only a minimal deflection of the vibrating string took place. On listening, no sound

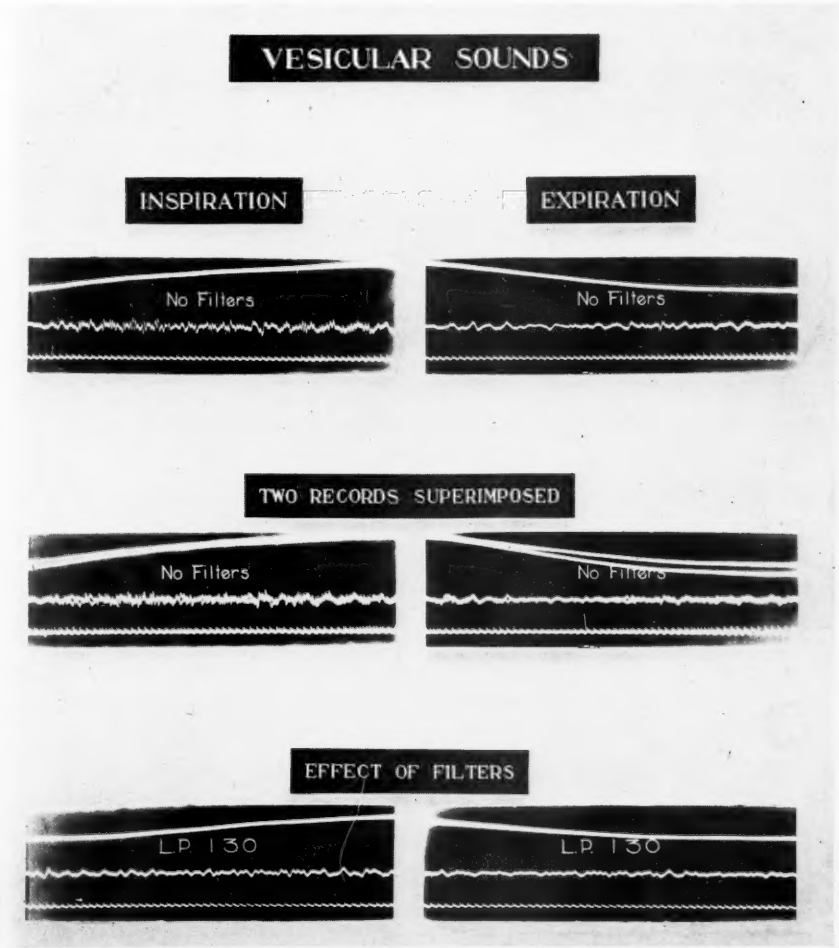

CHART 4. VESICULAR BREATH-SOUNDS, TAKEN POSTERIORLY IN 10TH INTERSPACE

Upper pair of curves: On inspiration, frequency of vibrations (pitch), amplitude (loudness) and total duration greater than on expiration. Frequency-counts given in text.

Middle pair: Patterns of oscillations in two different records superimpose with close agreement throughout both phases of respiration.

Bottom pair: Small but definite oscillations appear on introducing low pass 130 filter. More marked in inspiration than expiration. Inspiration barely audible on auscultation.

could then be heard. This occurred at all manometric readings, and stands in contrast to corresponding results of the effect of the low pass 130 filter in tracheal breath-sounds, when taken without interposed lung tissue. At relatively high pressures in the sheep's lungs the pulse from the throat of the subject who was breathing was often identified by its characteristic deflections which recurred at the proper intervals on the original long film. It is indicated on the charts by a star.

In chart 4 some records of vesicular breath-sounds from the same individual are reproduced. The subject sat on a stool instead of lying recumbent. The transmitter was held against the chest-wall at a pressure which made the sounds loudest when heard through the electrical stethoscope, instead of resting against the skin under its own weight. Otherwise the procedure was the same as in the other experiments. The site chosen for obtaining the vesicular sounds was the right 10th interspace posteriorly, usually slightly lateral to the angle of the scapula. The amplitude of the oscillations is rather small but is greater in inspiration than in expiration, as expected. The same is true of the wave-frequency. A count shows 77 to 500 vibrations per second on inspiration and 55 to 250 on expiration.

On inspiration two peaks appear on a distribution-chart of frequencies, one between 83 and 125 with the highest point between 100 and 111 vibrations per second, the other between 200 and 500 per second. A similar chart for expiration shows relatively few waves in the sample, so that there is no real peak but merely a scattering between 90 and 160 vibrations per second. In all the records of vesicular inspiration taken on this individual, very long waves (some 30 per sec.) uniformly appear near the end of each inspiratory movement. Two different records from the same individual are superimposed to show the close similarity in pattern of the deflections, as a matter of reproducibility. Finally, introduction of the low pass 130 filter still allows appreciable movements of the vibrating string to take place. In comparison with the results without any filters, there is a distinctly greater component below 130 vibrations per second in the case of the vesicular breath-sounds than in any of the records taken over sheep's lungs, but the amplitude of those low-pitched oscillations in vesicular breathing is nevertheless somewhat less than that of waves below 130 vibrations per second in the tracheal breath-sounds.

DISCUSSION

Exenterated lungs were chosen for these experiments with the hope of eliminating some of the variable factors which complicate studies of the chest in living subjects. It is of course recognized that death alone will bring on rapid changes in body tissues and accordingly may change the vibrating system of lungs. However, it is felt in the present situation that the outstanding points of our records are not unduly influenced in that way. The time between death of the animal and the beginning of our experiments was shortened to from 30 to 40 minutes, and furthermore the lungs were kept moist and warm during that time. If the elasticity of the lungs can be considered an indication of their utility for the study of sound-transmission, our preparations served the purpose, because all those lungs which form the basis of this report collapsed spontaneously after inflation at the close of each experiment. If the lungs were then allowed to stand uncovered for, say, an hour or so longer, they no longer retained their former collapsibility.

The initial aim in this undertaking was to vary only the air-pressure in a lung and then to register its effect on a sound transmitted through the lung. Consequently, any flow of gas into and out of the alveoli was considered undesirable, and so the lung was kept immobile during each observation. It is obvious that, even if all other variables are eliminated, a change of air-pressure alone produces more than one effect on the preparation. The walls of the alveoli are stretched, and fewer of them make up that particular portion through which the sound passes. Not only the density of the lung but also its elastic tension, perhaps also the factor of friction in the tissue, are accordingly altered. No attempt is made to assess any of those functions separately. The resultant effect alone is offered as a series of units in which pressure is varied and volume kept constant.

Tracheal respiration was selected as the source of sound, because it has the requisite high and low-pitched components, and also because it brings the experiments closer to the conditions met in the practice of medicine than would occur if an artificial sound-box were used. To be sure it is hard to control the exact intensity of any breath-sounds in a living subject. However, it is believed that more is gained than lost. Reproducibility of results has been used as the test. Frequency and amplitude of the waves gave close agreement, not only when taken directly from the throat or from the base of the chest of the subject, but

also when different lungs were interposed between throat and transmitter on different days, after the technique of procedure had once become final and smoothly established. As a single example, two films, taken at the same level from the base of the chest but not from identically the same spot, are shown on chart 4. The type of deflection coincides throughout both phases of respiration. These films are chosen because the vesicular sounds have been considered here to be the most difficult to obtain with reliability. Finally, in addition to the standard of satisfactory reproducibility, the validity of these results is not pushed beyond gross differences which appear well within the limits of likely error.

The records which are offered in this report confirm Martini's conclusions (2) in large part. The decrease in amplitude of transmitted vibrations with increasing pressure in the lung makes the higher-pitched sounds (above, say, 400 vib. per sec.) much less loud when heard on auscultation. This decrease goes on to total elimination of waves of high frequency as the air-pressure in the lung becomes greater, but this is not so striking on these charts as the ear would lead one to believe. The fact that high-pitched sounds appear relatively loud to the ear, when the actual amplitude of the physical vibrations is the same as that of a lower-pitched note, undoubtedly plays a part. A rapid decrease merely in the loudness of high-pitched components can readily be interpreted, when heard, as a lowering in pitch of the sounds as a whole. It is certain, then, that inflation of a lung will cause transmitted tracheal breathing to sound the lower in pitch, the higher the air-pressure in the lung. This is due to a change in the higher-wave-frequencies. That change, however, seems to be actually a decrease in their intensity rather than their total suppression, although both may take place. The emphasis is now made on quantitative relationships of amplitude and frequency of sound-waves transmitted through lungs under the conditions of these experiments.

The effect of the low pass 130 filter brings out a few interesting results in the case of the individual who was the subject in these investigations. In the first place, the records uniformly show appreciable oscillations in the neighborhood of and below 130 vibrations per second in tracheal and in vesicular respiration. In both cases it is more marked in inspiration than in expiration. On the other hand, introduction of the low pass 130 filter produces virtual suppression of all breath-sounds transmitted from the trachea through immobile sheep's lungs, whether they be collapsed or inflated. However, the filter does not suppress the low-pitched sounds

from the arterial pulse of the throat, when the interposed sheep's lung is expanded under pressures above some 14–16 cm. of water.

These results bear on certain arguments offered in regard to the origin of the vesicular sounds. Bushnell (7) has developed the proposition that vesicular breath-sounds originate in the larynx, where both high-pitched and low-pitched elements are produced. According to him, the deeper laryngeal components are forced on the lungs and give rise to the vesicular murmur as a result of being "amplified by the thorax as a resonator." Electrical filters substantiate the presence of high and low-pitched components in tracheal breathing. In fact, the extent of the deflection of the vibrating string, when only oscillations of about 130 a second or less are passed, came as a surprise to the writers, since sound was not heard through the stethoscope with a proportional loudness. It took several repetitions and control films to be convincing. On the other hand, practically no vibrations at and below 130 per second were transmitted through the lung-tissue which was placed directly on the larynx, regardless of the manometric pressure of the air in the lungs. It would seem that such minimal vibration at those low frequencies would be insufficient to effect any amplification at all from the thorax, even though the latter act as a very efficient resonator.

The theory of an intrathoracic origin of the vesicular murmur has much in its favor. The latest article, which has come to our attention as a review of the matter from this standpoint, is written by C. M. Montgomery (8). One of the leading arguments presented by him relates to a fundamental difference between laryngeal sounds and those which are heard through the chest-wall. The tracheal sounds are described there as higher-pitched, louder, and longer in expiration than in inspiration, in contrast to the vesicular breath-sounds. This view is certainly correct so far as the total composite sounds are concerned. But some of the force is perhaps taken from this conclusion by the results obtained when the high frequencies are filtered out and only the lower-pitched elements of the tracheal breathing are registered. Then it is seen that those frequencies which are recognized as typical of the vesicular murmur,—about 108 oscillations a second, as given by Müller (9),—appear in very much the same ratio of intensity and duration in the tracheal breath-sounds, of which they are demonstrated here to be components, as they do in vesicular respiration.

In this report the most direct bearing on the origin of respiratory

sounds relates to the presence or absence of oscillations of low frequencies, using the low pass 130 filter to determine it. When an immobile sheep's lung is interposed between the trachea and the transmitter, vibrations of low frequency are not in evidence. Air does not move back and forth in the bronchial tree and lung of the sheep. Vibrations are merely forced on the lung as a passive system. However, the same filter applied to the living person whose lungs are expanding and contracting in normal respiration allows low-pitched sounds to register on the films as definite deflections, which are to be expected in typical vesicular breathing. The presence of these oscillations which come through the low pass 130 filter seems to require respiratory movements and, presumably also, a flow of air-currents back and forth in the pulmonary system.

SUMMARY

1. Graphic records of tracheal breath-sounds were obtained by direct contact of a microphone with the throat of a normal, adult, male individual. Without filters, the records correspond to the tracheal respiratory sounds as heard on auscultation. When vibrations above approximately 130 per second were suppressed with a filter, a definite series of slower oscillations of relatively small amplitude remained. These oscillations were more marked in inspiration than in expiration, in contrast to the proportions existing in the high-pitched components of tracheal sounds.

2. Freshly exenterated sheep's lungs were placed between the throat of the same individual and the microphone. The thickness of interposed lung substance was always kept at 4.5 cm. but the air-pressure in the lung was varied. With increasing pressure in each sheep's lung, the tracheal sounds which were transmitted through it decreased rapidly in loudness (amplitude of vibrations) and also in pitch (frequency). High-pitched sounds were chiefly involved.

3. When the low pass 130 filter was introduced, no appreciable deflection of the vibrating string appeared on the records of tracheal sounds transmitted through sheep's lungs, regardless of the pressure at which they were inflated.

4. Vesicular sounds were recorded from the 10th interspace posteriorly on the right side of the same individual. They appeared relatively low-pitched, with inspiration louder than expiration, as expected. Slight but definite vibrations were passed by the low pass 130 filter.

5. It is suggested that a current of air into and out of a lung may be necessary to effect the transmission of vibrations of low frequency.

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SOME SOURCES OF ACID-FAST BACILLI[1]

STEPHEN J. MAHER

I

The normal rod-forms of spore-bearing bacilli are non-acid-fast; when forced to grow in difficult media, as butter, the rods of anthrax and subtilis have been infrequently made acid-fast. The young spores of spore-bearing bacilli are usually non-acid-fast; most old spores of spore-bearing bacilli are acid-fast. Non-acid-fast spores of the subtilis group of bacilli, when forced to grow in the difficult medium of normal salt solution, develop polar beads, and then break up into non-acid-fast cocci. These cocci can be easily grown pure in subcultures, first, at room-temperature on slightly hypersaline bouillon, and later on all media and at 37°C.

Acid-fast spores of the subtilis group of bacilli, when forced to grow in the difficult medium of normal salt solution, usually lengthen slightly, and some of them develop acid-fast or non-acid-fast polar beads, and usually a few lengthen out into granular acid-fast rods. If the tubes in which this change has taken place be kept undisturbed for two weeks at room-temperature, or four to six days at 37°C., but preferably sealed, there will be found in many of them, mixed with non-acid-fast spores, beautiful clumps of acid-fast coccoid, ovoid, and rod forms, and no acid-fast spores.

By a careful use of slightly hypersaline albuminous or gelatinous media, or, better yet, by the use of hard slants of white of egg and serum (human or sheep), these acid-fasts may be obtained in pure culture. They resemble the acid-fasts that have been isolated from infusions of grass, and from butter and milk and various other sources. The acid-fast

[1] This paper was read at the Seventh International Tuberculosis Conference, held at Philadelphia, September 26, 1908. The text was then published in the *Report* of the Conference, now perhaps a sadly neglected and forgotten volume. One of the outstanding developments of the last few years has been the recrudescence of interest in the biology of the tubercle bacillus and a renewed searching of orthodox opinions that this has given rise to. The present swelling literature on "granules," "filterable forms" and "life-cycles" of the tubercle bacillus encourages the author to suppose that republication of his old communication might not be untimely. He is also desirous of reproducing the illustrations of the various microörganisms, which have never before been published.

rods from the first gelatine cultures are often as slender as smegma bacilli, or tubercle bacilli. If subcultures from the original growths in the hypersaline media be made on ordinary media, the acid-fasts will disappear and a pure culture of subtilis result. In milk a few swollen acid-fasts will persist for one or two generations, but they will finally disappear. However, after the acid-fasts have been grown for a few generations on a serum-and-white-of-egg medium, they can be readily grown pure on the glycerinated and other media on which the tubercle bacilli and the acid-fasts from the infusions of grasses and from butter and milk grow best.

II

If *Bacillus coli communis* be grown for a few weeks in plain bouillon, and then the bouillon be drawn off and sterile normal salt solution poured on the bacterial sediment, it will be found, after a few days, that the bacilli show a tendency to form into clumps, and in the centre of almost every clump there will be discernible one faintly acid-fast granule or coccus or rod. If now the fluid in the tubes be again drawn off and fresh normal salt solution substituted, most of the individual colon bacilli in the clumps will be found, after a few days, to have lost their outlines and to have fused together about one or more strongly acid-fast cocci. Subcultures on most ordinary media will give only vigorous non-acid-fast colon bacilli,—vigorous enough to penetrate and break up glycerine-agar. Subcultures from the salt solution containing the acid-fasts, made at room-temperature on serum-and-white-of-egg medium and on potato, will give red and yellow growths of colon bacilli, of which one-half or more of the organisms will be acid-fast. Subcultures on serum-and-white-of-egg at 37°C. will be reddish, but will contain no acid-fasts. *Bacillus typhosus* and *Bacillus proteus vulgaris*, subjected to the same technique, often develop acid-fast granules, first in individual rods and then in the centre of clumps, but I have not been able to cultivate acid-fasts from either of these organisms.

III

If tubercle bacilli, grown for a year or more in air-tight flasks of glycerine-bouillon, be subcultured on solid or liquid media, not air-tight, in some of the tubes there will be no growth; in others a very weak growth of tubercle bacilli; while in others, in which at first there seem to be no growth, the crumbs of the plant will slowly develop a reddish or yellowish

hue and begin to spread. Subcultures will give in one to four days pure growths of more or less acid-fast rods and cocci, corresponding in shape and size and staining characteristics to the acid-fasts grown from the infusions of timothy grass and developed from the spore-bearing bacilli, and from the colon bacillus. These more or less acid-fast derivatives of tubercle bacilli, of which I have now two strains from human tubercle bacilli, and one from avian tubercle bacilli, are probably genetically related to the non-acid-fast tubercle bacilli of Auclair and of Arloing and Courmont, and described by them several years ago.

IV

Plants made in glycerine-bouillon from the softening centres of carcinomatous nodules, which on direct smear show no bacterial forms, but only cells packed with the so called cancer bodies, will give after four days clumps of round and ovoid bacterial forms, and in the centre of every clump will be one or more acid-fast forms. The picture will be identical with that of the first appearance of acid-fast individuals in clumps of colon bacilli.

I have grown a pure culture of acid-fast cocci from the deeper cells of a facial epithelioma, and I have invariably been able, either on smears or by cultures, to find acid-fast forms mixed with outnumbering non-acid-fast forms in many kinds of superficial cancer. From two cases of uterine cancer, one a recurrence, I have grown pure cultures of a granular rod, faintly acid-fast or non-acid-fast, which I am convinced is a developmental form of the ordinary acid-fast smegma bacillus. And, in fact, by a little sophistication on difficult media it can be made acid-fast, but not again slender and short as the smegma bacillus. Even in its non-acid-fast form it crackles in the flame like the tubercle bacillus and all other acid-fasts. All these acid-fasts from cancer slowly curdle milk, and become less and less acid-fast and then die.

CONCLUSIONS

1. The acid-fasts are forms of ordinary bacteria which, the better to resist an unfavorable environment, have developed waxy capsules; or they are forms which have resulted from the stimulation of acid-fast spores in an environment unfavorable to the full or ordinary evolution of these spores.

2. Old tubercle bacilli, when suddenly transferred from an atmosphere

saturated with their own ethers to one to which there is access of air, often grow wholly or partly free of their waxy capsules, and as rapidly as the so called pseudotubercle bacilli.

3. Acid-fasts are to be found in, or can be cultivated from, several kinds of cancer. In internal cancer they resemble the acid-fast colon bacilli, and in uterine cancer the acid-fast smegma bacilli, and in cutaneous cancer either these same smegma bacilli or the coccal and ovoid acid-fasts derivable from spore-bearing bacilli.

4. A striking and perhaps significant difference between the tubercle bacillus and ordinary acid-fasts on the one hand, and the acid-fasts derivable from the colon bacillus and from cancer on the other hand, is that the latter curdle and redden litmus milk, while the former, as a rule, do not change it.

Explanation of Plates

All these drawings were made in 1908 for the author by Dr. Dwight M. Lewis from actual microscopic fields of the author's laboratory preparations.

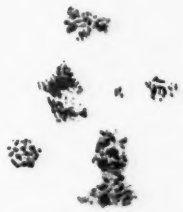
PLATE 1

Acid-Fasts from Cancer

For the significance of this plate see text.

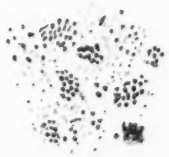
Acid-Fasts From Cancer.

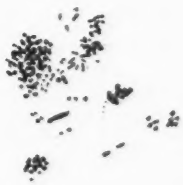
Facial Epithelioma. Facial Epithelioma. Facial Epithelioma.

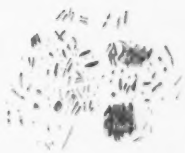


Glycerin-agar. 17 Days. Milk 1 Week. Glycerin-bouillon. 10 Months.

Carcinoma Uteri. Carcinoma Uteri. Carcinoma Uteri.







Glycerin-agar 15 Days Milk 1 Week. Glycerin-agar 17 Days.

PLATE 1

PLATE 2

Acid-Fasts Developed from Well-Known Non-Acid-Fasts

This plate is self-explanatory. The most dramatic of the transmutations here depicted is that of the acid-fast bacilli which I developed from spores of *Bacillus subtilis*. This strain continues to grow in gray subcultures true to its acid-fast form and frequently it still suggests a relationship to the bovine tubercle bacillus. Just now it grows best at room temperature. The acid-fasts from *Bacillus mycoides* and from *Bacillus coli communis* were also developed by the author. See text.

Acid-Fasts Developed From Non-Acid-Fasts.

B. Mycoides.

L. Serum. 17 Days.

B. Mycoides.

Milk. 3 Weeks.

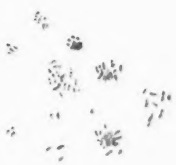
B. Mycoides.

Glycerin-agar. 3 Months.

B. Subtillis

Glycerin-agar. 17 Days.

B. Subtillis.



Milk. 1 Week.

B. Subtillis.

Glycerin-agar. 3 Months.

B. Coli Communis.

Egg-serum. 1 Month.

B. Coli Communis.

Milk 1 Month

B. Coli Communis.

Potato. 1 Month.

PLATE 2

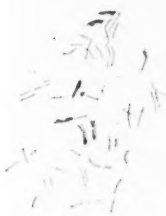
PLATE 3

Classical Acid-Fasts

"Binot" is the acid-fast isolated from the butter of Paris by Binot; "Grassberger" is the acid-fast isolated from oleomargarine by Grassberger; "Moeller's Timothy" is the famous acid-fast grown in 1898 by A. Moeller from the grass at Görbersdorf.

Classical Acid-Fasts.

Binot.



Glycerin-agar 17 Days.

Binot.

Milk 1 Week.

Binot.

Glycerin-agar. 3 Months.

Grassberger.

Glycerin-agar 5 Weeks.

Grassberger.

Milk 1 Week.

Grassberger.

Glycerin-agar 3 Months.

Moeller's Timothy.

Glycerin-agar. 17 Days.

Moeller's Timothy.

Milk 1 Week.

Moeller's Timothy.

Glycerin-agar. 4 Months.

PLATE 3

PLATE 4

Classical Acid-Fasts

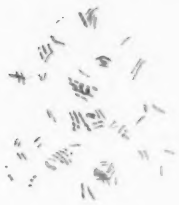
"Tobler I," "Tobler III," and "Tobler V" are strains developed from various samples of the butter of Zürich by Madame Marie Tobler. "Tobler I" is a facultative anaerobe. My original cultures of these classical acid-fasts depicted on plates 3 and 4 were given to me in 1905 by Dr. Binot of the Pasteur Institute of Paris, himself at that time one of the first and best students of the problem of the acid-fasts.

Classical Acid Fasts.

Tobler I

Glycerin-agar. 17 Days.

Tobler I



Milk 1 Week

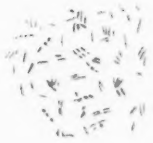
Tobler I

Glycerin-Agar 3 Months

Tobler III

Glycerin-agar. 17 Days.

Tobler III



Milk 1 Week

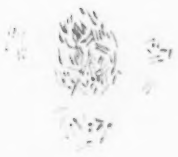
Tobler III

Glycerin-agar 3 Months.

Tobler V

Glycerin-agar. 17 Days.

Tobler V



Milk 1 Week.

Tobler V.

Glycerin-agar. 3 Months.

PLATE 4

PLATE 5

Acid-Fasts from Old Cultures of Tubercle Bacilli

The word "red" on this plate means that the degenerate strains of tubercle bacilli from which the smears were taken had developed chromogenesis and that grossly their cultures were of a more or less reddish hue.

Acid-Fasts From Old Cultures of Tubercle Bacilli.

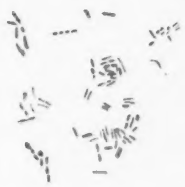
Red Human.

Glycerin-agar. 16 Days. 37°

Red Human.

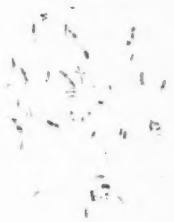
Glycerin-agar Room temperature

Red Human



Milk 37°

Red Human

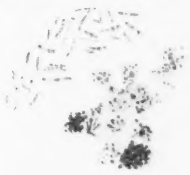


Milk. Room temperature.

Red Avian.

Glycerin-agar 37°

Red Avain
Glycerin-agar Room temperature
5 Weeks



Glycerin-agar. Room temperature
3 Days

Red Avian.

Milk. 37°

Red Avian

Milk. Room temperature

PLATE 5

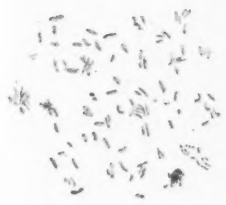
PLATE 6

Tubercle Bacilli

This plate needs no comment.

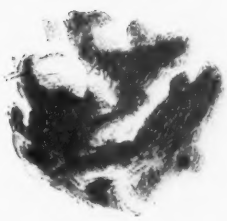
Tubercle Bacilli.

Human



Glycerin-agar. 3 Weeks.

Human



Milk 1 Month.

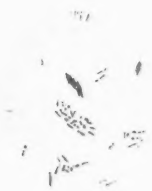
Human
Glycerin-bouillon.

17 Months.

Bovine

Glycerin-agar 14 Days.

Bovine.



Milk 4 Days.

Bovine
Glycerin-bouillon.

17 Months.

Avian.

Glycerin-agar. 3 Weeks.

Avian.

Milk 1 Week.

Avian
Glycerin-bouillon

17 Months.

CANCER OF THE LUNGS

FREDERICK L. HOFFMAN

The increasing frequency of lung cancers is at last attracting a fair measure of qualified consideration. It is probably one of the most suggestive aspects of the modern cancer problem in that it clearly visualizes the menace of malignant affections resulting obviously or obscurely in some way from our present-day mode of life. It is true that the increase in lung cancers may be more apparent than real and there are those who are inclined to attribute the increase essentially to improved diagnosis and the growing practice of autopsies, at least in modern hospital experience. But the same argument is brought against every other form of cancer apparently on the increase in modern civilized countries. As yet no writer on the subject seems to have examined exhaustively the general facts of the situation, the matter being usually dealt with on the basis of fragments of evidence, which, however, unmistakably draw attention to a problem of great seriousness. Unfortunately for many countries and localities, the cancer mortality data are only presented on the basis of the usual six groups in accordance with international classification. This method of statistical presentation completely obscures the essential new facts of the cancer problem which, for its adequate presentation, requires a much broader classification of certainly not less than thirty separate divisions if practical results are to be obtained.

The first attempt to present a comprehensive statement of cancer mortality for this country was made in a special report for the year 1914, published by the Census Office. In that year, out of 52,420 deaths from all forms of cancer, 371 were attributed to cancer of the lungs and pleura. The equivalent proportion was 0.7 per cent, or at a rate of 0.6 per 100,000 of population. But ten years later, or for 1924, the number of recorded deaths from cancer of the lungs and pleura was 1,586, equivalent to a proportion of 1.7 per cent, or at a rate of 1.6 per 100,000 of population. Here then is unmistakable evidence of a very decided apparent increase in frequency, which in any event may be accepted as proof that lung cancers are of much more common occurrence than is generally assumed to be the case. But it subsequently shows additional evidence suggestive

of the conclusion that the apparent increase is to a considerable extent a real increase in the relative frequency of occurrence of this form of malignant tumor.

Our American statistics are amply supported by statistics for England and Wales. For the male population of that country, the death-rate for cancer of the lung and pleura during the decade 1901–1910 was 1.0 per 100,000 of standardized population. For the decade 1911–1920 the corresponding death-rate was 1.34, but during the year 1926 the rate reached 2.33. In curious contrast, however, for the female population the rates changed from 0.75 for 1901–1910, remaining at the same figure for 1911–1920, to 9.2 during 1926. Unfortunately no corresponding death-rates by sex are available for the United States death registration area. But in connection with the San Francisco Cancer Survey, a considerable amount of information has been collected for certain cities of the United States and certain provinces of Canada, which throw additional light on the present situation.

That the increase has continued in this country is shown by the statistics for 1925 and 1926. In 1925 in the United States registration area, there occurred 1728 deaths from cancer of the lung, equivalent to a rate of 1.7 per 100,000. During 1926 the corresponding mortality was 1892, while the rate was 1.8. It is, therefore, safe to conclude that the normal frequency of cancer of the lungs throughout the country is less than 2 per 100,000 and that any figure above that average must be accepted as an excessive indication of local frequency demanding particular consideration.[1]

In the following observations the mortality for a period of years has been combined to yield average results of greater trustworthiness. For Albany, New York, for example, for 1919–1923, the rate for cancer of the lungs was 2.5. For New Orleans for 1919–1923 for the white population the rate was 2.8, and for the colored, 0.6. For San Francisco for 1920–1924 the rate was 4.7. For Boston for 1920–1924 the rate was 3.9. For Chicago for 1924 the rate was 2.8, and for 1925, 2.0. For Buffalo for 1922–1926 the rate was 3.2. For the Province of Alberta for 1921–1925 the rate was 1.3. For British Columbia for 1920–1924 it was 2.1. For the Province of Saskatchewan for 1920–1924 it was only 0.5, while for the city of Winnipeg for 1920–1924 it was 3.3.

[1] There was a further increase in the frequency of cancer of the lungs from 1,892 deaths in 1926 to 2,012 deaths in 1927, or an increase in the rate per 100,000 of population from 1.8 to 1.9. These returns are for the United States registration area which represents about 95 per cent of the entire country.

In most of these cities the male rate is above the average for both sexes combined. But the excess in the difference is not as marked in this country as in England.

The outstanding result of the foregoing analysis is the high incidence of cancer of the lungs in the city of San Francisco, where the average rate has been as high as 4.7, or nearly three times the normal for the country at large in 1925. Excessive rates also are shown for the city of Boston and the city of Buffalo, as well as for the city of Winnipeg.

One of the most exhaustive studies of primary carcinomas of the lungs has been contributed by Grove and Kramer, published in the *American Journal of Medical Sciences* for February, 1926. This is a clinical and pathological study from the Cook County Hospital, with a report of 21 necropsies and 3 biopsies. The authors point out in the introduction that "In reviewing the literature on primary carcinoma of the lung, one is struck by the fact that in spite of the marked increase in necropsy reports in the last few years, most writers still persist in calling the condition a rare one."

They refer to a paper by Barron in the *Archives of Surgery* for 1922, who observed that "It has almost been a tradition that carcinoma of the lung is an extremely rare disease, of negligible clinical importance, and that its antemortem diagnosis is practically impossible."

They also refer to an earlier paper by Adler, published in 1912, who mentioned primary malignant neoplasms of the lung as one of the rarest forms of the disease. Since 1917, however, the medical literature has contained an unusually large number of case reports, the majority of which are authentic, as they are accompanied by necropsy reports.

Grove and Kramer reviewed at length the available statistics of cancer of the lung, yielding widely varying results for different countries. As a rule, however, the proportion of cases of cancer of the lung amounted to less than 0.5 per cent of the whole.

The most recent addition to our knowledge is an extended paper on *The Statistics of Lung Tumors* by Ernst Schoenherr, published in the *Proceedings of the German Society for Cancer Research* for September, 1928. This gives statistics for the City Hospital near Chemnitz, based entirely on autopsy material. It shows that during the nine years 1919–1927, out of 1,002 cancer cases coming to autopsy, as many as 110, or 10.9 per cent, were lung cancers. The proportion increased from 10.2 per cent during the first three years to 10.4 per cent during the second three years, and to 11.6 per cent during the last three years. For 1927, in

fact, the proportion was as high as 13.4 per cent. It is observed that Chemnitz in the postwar period occupied the first position as regards lung cancers in Germany. No satisfactory explanation of this unusual condition has, however, been forthcoming. The local situation is possibly complicated by the nearby Schneeberg district in which lung cancers have for many years been unusually frequent, due to mining conditions. In my *Cancer throughout the World,* I give information on this phase of the subject which does not seem to require repetition on this occasion. Unfortunately, German statistical discussions are invariably confusing and complicated by the omission of proper headings to statistical tables, which makes a full use of the elaborate investigation by Schoenherr exceptionally difficult. Exceedingly rigorous reading is required to draw the best results from the mass of evidence presented. But every aspect of the problem is considered by this author, whose observations are deserving of being completely translated into English. Among previous diseases, influenza had rarely been present. Bronchial catarrh was observed, but not disproportionately to the whole. Bronchiectasis, which in recent years is claimed to have increased, was not observed as a complication. The same is true of serious lung affections. In only four cases was there a coincident lung tuberculosis, or 4.4 per cent of the total mortality from cancer of the lungs.

Of chief interest to the author were the results as regards nicotine absorption. He recalls observations by Seyfarch that bronchial carcinoma was a typical occupational disease of cigar-makers, but that in his own study of the subject he did not find a single cigar-worker among those who had died from cancer of the lung. In 36 cases there was no evidence of nicotine absorption, while in 29 cases 17 were excessive smokers, and 12 were nonsmokers or very moderate smokers. Of the 17 excessive smokers 7 were cigar-makers, one a cigarette-maker, and the others merely observed that they did not indulge excessively. There were 17 women patients among whom, of course, the question of smoking was difficult to ascertain. Schoenherr therefore admits that the question as regards the inference of smoking in cancer of the lungs remains undetermined.

It would carry me too far to examine critically into all the extended observations of this author, who, as I have pointed out, has made one of the outstanding contributions to the subject. He concludes, that for chemists at least, during the postwar period, a material increase in malignant tumors of the lungs has been established. He draws atten-

tion to the coincident increase in automobile traffic and the pollution of the air of large cities. Regardless of his thoroughness, however, his investigation on general principles has been productive of no practical results.

Referring back to the investigation by Grove and Kramer, a more definite picture is presented. Particularly as regards tuberculosis, these authors point out that

> Most authors, including Ewing, have given tuberculosis as the chief etiologic factor; yet in only 1 of our cases was any evidence of pulmonary tuberculosis found. This to us seems worthy of mention, because of the fact that more than one-half of the autopsies at the Cook County Hospital are performed on colored patients, and the ravages of tuberculosis among the colored race are well known. The fact that only 2 of the 24 cases here reported occurred in colored patients appears to be significant. In the past the greatest emphasis has been placed on the association of tuberculosis with carcinoma, although it seems to us with very little ground, and now the recent increase in primary lung tumors would further tend to support Rokitansky's dictum. Carmen stated that tuberculosis and carcinoma of the lung may exceptionally coexist, although in 17 autopsies no tuberculosis was observed.

These conclusions coincide with my own. Regardless of every effort to trace a more definite connection between lung carcinoma and pulmonary tuberculosis, I have failed to establish such a connection in even a few cases significant for the purpose. I have discussed the subject with outstanding authorities on the question, but all with negative results. Highly significant in this connection is the declining death-rate from tuberculosis, which has gone down about 50 per cent during the last forty years, while the mortality from lung cancers has rapidly increased during the same period.[2]

Nor is there any evidence that exposure to irritant gases has been productive of lung cancers as best illustrated during our experience with gas warfare. In the report on the *Medical Aspects of Gas Warfare*, published by the United States Army in its *Medical History of the War*, there

[2] The statement that cancer and tuberculosis rarely coincide requires material modifications. I have just found that the Census Office for 1925 has fortunately made an elaborate analysis of joint causes of death. On examining this report I find the following interesting results. There were out of 95,504 deaths from cancer, 273, or one in 357, complicated by some form of tuberculosis mostly of the pulmonary form. This is a much larger proportion, I am sure, than has generally been assumed to occur. Yet the results are not based on autopsy findings in most cases but chiefly on clinical diagnosis.

is no mention of lung cancers as the result of lung irritants, although the experience was on a very extended scale. At least my own examination of the volume has failed to reveal a single reference to lung carcinoma, although it is possible that obscure references have escaped my attention. The total number of admissions for gas poisoning in the experience of the American Expeditionary Forces was 70,552. Yet this immense experience seems not to have yielded, as far as I can find out, a single case of cancer of the lung, although 1,221 deaths occurred among the number admitted. I have carefully examined the causes of death of 546 deaths specifically analyzed, but while countless complications are given none is suggestive of cancer of the lungs. Since all of these deaths apparently came to autopsy, or at least a large proportion, the evidence would seem to be conclusive. The same applies to a fairly careful reading of the after-effects of gas poisoning, which are barren of any references to lung cancers unless an obscure statement has escaped my attention. This includes a careful reading of a summary study of 3,014 gas casualties dealt with in considerable detail.

As a matter of record, I include in this discussion the summary and conclusions in the investigation by Grove and Kramer as follows:

Primary carcinoma of the lung is not as rare a clinical condition as has been described in the past, and the condition can be diagnosed antemortem.

The striking increase in the number of tumors of the lung since the influenza epidemic suggests some relation between these two conditions.

Pulmonary cancer presents a very varied pathologic picture, not only as to gross and microscopic characteristics, but also as regards the associated pathology. Metastases occur early and are very widespread.

Histogenesis presents many difficulties, because of the morphological variations in the cells concerned and the difficulty in obtaining the tumors in the early stages for study.

Efforts to classify these tumors as to histogenesis admit great probability of error. However, from authentic studies it appears that origin from bronchial mucosa is most frequent and that origin from alveolar epithelium is very rare.

There are no pathognomonic symptoms of tumor of the lung; weakness, cough, expectoration, pain in the chest and dyspnea being most important.

With more frequent use of the bronchoscope and with an appreciation that primary carcinoma of the lung is not rare, this clinical entity will be diagnosed more commonly antemortem.

The use of the bronchoscope both for diagnosis and treatment opens a field in a condition where formerly the prognosis was very poor.

The next important discussion to which attention may be drawn is an address delivered before the *American Medical Association* in 1927 by McCrae, Funk and Jackson of Philadelphia. As regards the increase in frequency, with which I am chiefly concerned, these authors observed as follows:

> The older statistics, which represent primary carcinoma of the lung as occurring in less than 1 per cent of all primary carcinomas, are apparently too low for the present. Recent statistics from Hamburg and Leipzig reveal at times an incidence as high as 9.4 and 15.5 per cent for primary carcinomas originating in the lungs. Kikuth reports that in Hamburg pulmonary carcinoma ranks second, being one third as common as gastric carcinoma. Staehelin of Basel reports a rate of 5 per cent from 1912 to 1924 as compared to 1.7 per cent before 1906, and Berblinger of Jena, an incidence of 8.3 per cent in the period 1920 to 1924 as compared to 2.2 per cent in 1910 to 1914. There is no experience in this country which compares with these observations. Nevertheless an increasing number of reports suggest a greater relative frequency of primary lung cancer than has heretofore occurred. In the Jefferson Hospital during the last three years there have been 621 necropsies, with fifty-three instances of carcinoma, of which four have been primary in the lung. All of these have been considered as originating in the bronchi.
>
> The cause or causes of the increase in lung carcinoma have not been determined. The suggestion that the inhalation of particles of tar and the irritation of gasoline fumes play a part has to be seriously considered. The frequency of the antemortem diagnosis, in spite of the improvements of clinical methods, falls far below the postmortem frequency. We believe that with an increased clinical interest in a disease which is not uncommon more accurate diagnoses are possible. Adler's monograph, which appeared in 1912, did much to stimulate the clinical interest.

I regret that I am unable to give an extended return of the age-incidence of cancer of the lung. The facts do not appear to have been tabulated by the Census Office nor by the English Registrar-General. I find that according to the investigation by McCrae, *et al.*, the distribution of the deaths from cancer of the lung at various ages was as follows: "Approximately nine tenths of the patients are past 35 years of age. Males seem to predominate in the proportion of four to one in the combined series."

Mention is made of Weller's series of cases, in which there were 70 males and 17 females among 87 patients. In the present series there were 96 males and 22 females. The same authors emphasize the loca-

tion of the tumor which was found in the right side of the lung in 40 per cent, in the left side in 47 per cent, and in both sides in 9 per cent, aside from 4 per cent in which the site was not clearly established. I might have pointed out in this connection that, according to Grove and Kramer,

> Adler, in a study of 374 collected cases, found 188 of the cancers in the right lung and 157 in the left lung. Weller, in an analysis of 89 cases, found the right and left sides affected with equal frequency. Barron stated that the right lung is affected more often than the left, and the upper lobe more frequently than the lower.

Evidently a much larger number of cases is required for the ascertainment of trustworthy averages, if indeed their occurrence in one lung or another is not a matter of pure chance.

I add to the foregoing the conclusions of McCrae, *et al.*, as follows:

> 1. The evidence suggests that carcinoma of the lung, which in the majority of cases originates in a bronchus, is increasing in frequency.
> 2. These bronchial tumors appear to have a relatively low malignancy, and hence the hope that early diagnosis and intensive roentgen-ray therapy may be effectual in at least prolonging life.
> 3. Early diagnosis should be made if the possibility of bronchial neoplasm is considered and careful studies are made. The early symptoms are usually those of bronchial irritation and the early signs those of bronchial obstruction.
> 4. By bronchoscopy a positive diagnosis can almost always be made promptly and proper treatment instituted.
> 5. Patients who present obscure pulmonary and bronchial symptoms have a right to the benefit to be derived from bronchoscopy.

As regards the difficulties of an accurate diagnosis, I cannot do better than quote the following observation by Dr. Charles L. Minor of Asheville, North Carolina, supplementing his discussion of the paper by McCrae, *et al.*, as follows:

> It has been impressed on me frequently that we do not think sufficiently of possible malignant conditions in these roentgen-ray pictures. Only a year ago I saw a case that had been studied in two university clinics in the United States and in other places, and yet the malignant nature of the growth was overlooked. I was convinced that it was a case of tuberculosis, although I was unable to find the bacilli. The general practitioner cannot afford to neglect chronic cough as he has done in the past. That some of these chronic

coughs are nontuberculous is true, but it is hard to say how many examinations must be made before one can be sure that the cough is not tuberculous.

The incidence of intrathoracic tumors, with particular reference to Manchester, England, was dealt with in an extended paper published in the *Lancet* of July 16, 1927, contributed by Dr. J. B. Duguid, who observed by way of introduction that "Most of those who have had recent experience of the post mortem work of the Manchester Royal Infirmary have formed an impression that the incidence of intrathoracic tumours there is high." He therefore remarks that

> This has led to the suggestion that air pollution, which is exceptionally great in Manchester, may be a factor in the production of these tumours. In various other centres, both in Europe and in America, recent investigations have made it appear that the incidence has increased in late years, and it has been thought that a similar increase was noticeable in Manchester.

Duguid therefore made an examination of the registers of autopsies performed at the Infirmary since 1868 with the exception of the year 1910. The results of his investigation show as follows: From 1868 to 1885 the proportion of cancer of the lung was 0.24 per cent. It increased slightly with variations to 2.40 per cent during the period 1901–1905, while during 1921–1925 the percentage was 2.57. During 1926 there were 335 autopsies, of which 11, or 2.9 per cent, revealed cancer of the lung. Duguid points out the difficulties of drawing accurate conclusions from autopsy records which may be impaired by bias in seeking for unusual features and to press more urgently such cases. Or, as he observes, "The pathological conditions which are most common in man are not those most commonly revealed in the postmortem room." He draws attention to the fact that the percentage in the ward records tends to be lower than in the autopsy records, found approximately for a period of six years to have been 0.9 per cent, in contrast to 2.5 per cent for postmortems. Hence his conclusion that

> The fact that the percentage in the ward records tends to be lower than in the autopsy records seems to show that these latter are in no wise an accurate representation of the general incidence of the tumours. The high percentage in the autopsy records is probably in great measure due to the fatal nature of the disease.

Of interest is the sex distribution of 175 cases, of which 86.3 per cent were males and 13.7 per cent females. The age distribution also is of

interest, showing that 5 cases were under 21 years of age, while the majority occurred at ages 36–60. Twelve cases were 61 years of age and over, one being between the ages of 71 and 75. The right lung was affected in 78 cases, the left lung in 67 cases, both lungs in 18 cases, and no lung involved in 12. The occupational distribution is also inconclusive. Of 143 male cases, the largest number in any single occupation was found among laborers and of these there were 28. Next to these in order of numbers came carters, of whom there were 9, and clerks, numbering 8. In none of the other occupations were more than 4 cases recorded. Thus the number of men who described themselves as carters was striking, and this drew attention to those who registered occupations closely related in one way or another to that of carter. These totalled 25, and were as follows: Carters, 9; van-drivers, 2; lorryman, 1; coachman, 1; teamster, 1; horse-keepers, 2; hostler, 1; stableman, 1; tram-drivers, 3; engine-drivers, 2; team-guard, 1; railway-guard, 1. These represented all the transport-workers in the list, so that such workers constituted 16.55 per cent of all male cases. Unfortunately, it was found impossible to estimate with accuracy the number of outdoor and indoor workers, but it could be judged that at least 75 per cent of the adult population were indoor workers. Since, therefore, it is said,

> In the cases of tumour there were actually more outdoor workers than indoor ones, it may be concluded that the incidence is higher in the former class in a proportion of three to one. In the census list it was found that the transport workers constituted 12.34 per cent of the total male population, whereas in the case list these workers, as stated above, constituted 16.55 per cent of the male cases. In none of the other occupations were the numbers of cases large enough to allow of useful comparisons being made.

Hence the general conclusion,

> The value of these findings depends much on the question of the correct classification of the oat-cell tumours, or more especially on the question of whether or not they are tumours of the bronchi. If they are in reality bronchial cancers the findings would be more valuable since it would then be shown that the bronchi, and not the mediastinal glands, are by far the most important structures in regard to tumour growths of the thorax. In Manchester bronchial cancers, instead of constituting only about 37 per cent of thoracic tumours, would constitute considerably over 80 per cent of these. The single fact that so many of the tumours arise in a tissue which is directly exposed to the atmosphere would encourage the suspicion that atmospheric impurity may be an

important factor in their causation. Nevertheless it must be some specific constituent of the pollution rather than the general atmospheric pollution itself that should be suspected, because the atmospheric conditions in cities are generally supposed to be improved since the coming into operation of the Smoke Abatement Acts, and were it simply a matter of a smoke-laden atmosphere, the incidence of thoracic tumours would be expected correspondingly to be on the decrease. There is strong evidence from elsewhere that special external conditions, probably through the medium of the atmosphere, may be conducive to cancer of the lungs and bronchi. In the mining district of Schneeberg, in Saxony, it has been shown that the men who work amongst ores of cobalt, bismuth, and nickel are especially subject to these tumours. Arnstein notes that one third of all the miners admitted to hospital in that district in the years 1907–11 were admitted with a diagnosis of pulmonary cancer.

In Manchester the figures point to no particular industry as being dangerous in this respect, but rather to those who are outdoor workers as being more prone to thoracic tumours than those who work in more sheltered conditions. It has been noted, however, that carters and drivers are comparatively numerous in the list of those affected. Obviously no conclusions can safely be drawn from such findings alone and all that can be done is to cite briefly some possible reasons for men of that class being so frequently affected.

In the first place, men who work in the open and are constantly exposed to weather conditions in an excessively damp climate such as that of Manchester may possibly be unduly exposed to the danger of chronic bronchial catarrh, and it is conceivable that such irritation may be a factor in the production of bronchial cancer; full enough information regarding the past histories of the cases to settle this point cannot now be obtained. In the second place, men who are much on the roads are exposed to an atmosphere which is very often heavily laden with dust and particles of most varied materials, and it may be that materials of a similar nature to those responsible for the high incidence of cancer among the Schneeberg miners may also be present in road dust. A relationship between cancer of the lungs and conditions of the highways has been suggested by other observers. Staehelin has suggested that the modern custom of tarring roads is responsible for the increased incidence and others have cited pollution of the air by exhaust gases from motor-driven vehicles as being a possible factor.

Thus although the figures derived from Manchester are in themselves insignificant, they are of importance in so far as they yield evidence which is in concurrence with the propositions of other observers. In an article on Bronchiogenetic Carcinoma, R. V. Hudson recently drew attention to the high incidence of such tumours in grooms, suggesting at the same time that these men are susceptible because they are liable to inhale much dust during the process of grooming horses.

As a practical contribution, the preceding paper must be looked upon as one of outstanding importance. The *Lancet*, in an extended discussion of the subject, concludes that,

Giving all the weight they deserve to these criticisms of any numerical measurement which may be made, there is, we believe, ample evidence that the statement "cancer of the lung is considerably commoner than it used to be" is true. There seems also to be no doubt that it is much more frequent in men than in women—i.e., that is connected either with a male habit or with occupational rather than home life. Further than this it seems hardly possible to go at present; we hope that some of the cancer research organizations will take up the problem intensively, for it is evident that most important evidence can be obtained if the disease can be definitely traced to some mode of life. It should be possible to do this and various suggestive relationships have been put forward already. Dr. Duguid finds that a remarkably large proportion of his cases were occupied in one way and another with road traffic; road traffic as a whole has, of course, enormously increased but the emanations from motors, including particles of oil, and the use of tar on the roads, are obvious possibilities. Experimentally, tar and other products of the combustion of coal have a unique carcinogenic efficacy, and Dr. A. N. Kingsbury has recently attributed a scrotal epithelioma in a Tamil to the irritation of oil sprayed in antimalarial operations. Tobacco smoking is much more prevalent than it was, and it is one of the signs of the times that the class from which general hospital patients are mostly drawn have changed pipes for cigarettes. Dr. E. Frommel, in an interesting paper on their experience in Geneva, attributes the greatest importance to a dusty occupation, and his data seem to show that vegetable dusts (as in woodmaking) are as important as mineral particles. The suggestion has been made that the increase in pulmonary cancer is due to the 1918–19 epidemic of influenza. If that is so, there should later on be a corresponding decline in frequency. But while we wait for time to answer that particular question it is most desirable that a concerted attack should be made on the whole problem—the more so because it seems likely that it is in large part soluble.

To make the foregoing statement as complete as possible, I add a brief note on the observations of Frommel reported in the *Revue de Médicine*, 1927, in part as follows:

From 1900 to the end of September, 1926, 41 cases of pulmonary cancer in which the diagnosis was verified after death were admitted to the medical clinic of Geneva University. Of these 40 were examples of carcinoma and 1 of sarcoma of the Schneeberger type; 30 occurred in men and 11 in women.

The ages of the patients ranged from 27 to 91 years, the average being 58. Frommel concludes, therefore, that cancer of the lung is an affection of the second half of life, the male sex being principally affected. Among 40 cases in which the history could be elicited, 30 patients had suffered from other lung affections before cancer developed. Pulmonary tuberculosis had been present in 8 cases, in 6 of which it was found in the same lobe as the cancer, thus showing that the two processes are not incompatible with one another, as Rokitansky maintained. Frommel adds that there is evidence, on the other hand, that pulmonary tuberculosis acts as a chronic irritant and favours the development of cancer. Chronic bronchitis, bronchiectasis, or emphysema was present in 22 patients, so that their lungs were in a condition of diminished resistance. The part played by dust in the precancerous state is illustrated by the fact that out of 29 engaged in a definite occupation 22 were exposed to the inhalation of mineral or vegetable dust.

Those who are interested in Duguid's discussion should read a supplementary letter by Dr. Frank E. Tylecote in the London *Lancet* of July 30, 1927. He points out in his letter, among other interesting facts, that

As a clinician I have one or two other remarks to make: (1) It might be assumed that the incidence is limited mainly to the working classes. This is by no means the case; in Manchester we have lost several well-known public men from this disease in recent years. (2) I have no statistics with regard to tobacco, but I think that in almost every case I have seen and known of the patient has been a regular smoker, generally of cigarettes. To this there have been the following exceptions: (a) two ladies who succumbed to the disease unusually rapidly. In each case the lady lived "hard by" a railway station, where trains frequently stopped, and where smoke from the engines must have at almost all times pervaded both house and garden. (b) A group of acute adolescent cases, all males, in which I regard the condition as being usually mediastinal Hodgkin's disease.

Nor must I omit mentioning an important paper on *Primary Cancer of the Lungs*, being a clinical report of 17 cases by Lichty, Wright and Baumgartner, Clifton Springs, New York. I will only quote the introductory observation that

Carcinoma of the lungs in the most recent studies shows a much higher incidence than was formerly thought. It has come to be recognized as occurring comparatively frequently; so much so that in the consideration of diseases of the chest, especially of the chronic form, one should always hold in mind the possibility of primary carcinoma of the lungs.

These authors give the returns of 4,362 autopsies, of which 13 were found to be cases of carcinoma of the lung. But dividing the autopsies into three periods from 1899 to 1921, the proportion of such cases has increased from none during the first third of the period to 0.2 per cent during the second third and to 0.9 per cent during the last. For all cases the average was 0.29 per cent. In concluding the discussion of the paper, Dr. Lichty refers briefly to causative conditions as follows:

> As to etiology, we do not believe this matter is settled as being due to the epidemic of influenza of 1917 and 1918. Some authors have spoken of the possibility of gas from combustion engines, and coal tar in connection with the tar roads which are being built all over the country, and also of tobacco smoke as being the cause of increased carcinoma of the lung. These may be factors, but they certainly do not explain the increase of carcinoma in all parts of the body which have occurred as shown by our statistics at the same time that the increase in carcinoma of the lung has occurred. The suggestion of Dr. Barron, that the curve of cancer incidence is coming down, coincides with our experience. There are not as many cases of carcinoma of the lung or carcinoma elsewhere reported in the past year as there were two or three years ago. It is our feeling that the epidemic of influenza may have had no more effect on the increase of carcinoma of the lung than the terrific strain placed on the human race consequent to the Great War, which was at its height coincidently with the influenza epidemic.

The foregoing is a far from satisfactory presentation of an extremely important phase of the cancer problem. The evidence brought together is intended primarily to serve the purpose of drawing attention to the increasing seriousness of cancer of the lung and the practical certainty that the observed increase is real and not apparent. Evidence to this effect could be multiplied by reports from all over the world, but this would unduly extend the present discussion.

It may be summarized in the following statement. (1) Cancer of the lung is unquestionably increasing in modern civilized countries. (2) While no entirely conclusive evidence is yet available, there are reasons for believing that the increased frequency is in some way connected with the modern development of road transport and road conditions which aid in gross atmospheric pollution. (3) There is no definite evidence that smoking habits are a direct contributory cause toward malignant growths in the lungs. (4) The disease unquestionably demands more extended research consideration from every possible point of view. Particularly is this true of the urgency of more detailed studies of deaths

from cancer of the lung and of the more complete tabulation of all the clinical and pathological facts that bear upon the disease with which the patient is affected. (5) One outstanding conclusion upon which most writers seem to be agreed is that cancer of the lung is in some way connected with modern occupational or industrial development. (6) Gas warfare, however, as well as influenza, appear not to be direct contributory causes. (7) The relatively predominating number of men affected is highly significant. (8) The diagnosis of cancer of the lung is improving and there are some reasons for believing that this is also true of modern methods of treatment. (9) I agree with Heuer that with earlier diagnosis and earlier operative treatment the surgery of intrathoracic tumors may be greatly improved. (10) There is apparently no relation established between the occurrence of lung tumors and pulmonary tuberculosis.[3]

[3] Since this paper was prepared I have come in receipt of the proceedings of the International Conference on Cancer in London, 1928, which contains several interesting and suggestive papers on cancer of the lungs, including an analysis of 25 years' experience in British hospitals, giving a total of 53,750 postmortems, of which 710 cases were intrathoracic, or 1.32 per cent. These statistics are furnished by J. Shaw Dunn and C. Powell White of Manchester. There is also an unusually interesting and valuable discussion on *The Alleged Increased Frequency of Primary Carcinoma of the Lung* by Dr. Robert Hutchison of London, which shows an increase in the proportion of carcinoma of the lung cases in the total number of autopsies examined from 0.51 per cent in 1907 to 2.05 per cent in 1925. Based only on the total malignant neoplasms disclosed at autopsy, the proportion of cancer of the lungs increased from 1.0 per cent in 1907 to 3.7 per cent in 1925. Dr. Hutchison is of the opinion that he does not consider "this study lends much support to the theory that the increase in carcinoma of the lung is to be attributed to the great epidemic of influenza." He makes the further interesting observation that "As is well known a possible connection between pulmonary tuberculosis and cancer has also been much discussed. In this series of 139 cases, 47 showed some signs of tubercular infection of the lungs. In only six, however, was the disease active. It seems probable that the incidence of old tuberculosis lesions in these cases was not higher than it would be in a similar series of cases of any other disease." As shown elsewhere in a footnote, the proportion of cancer deaths in which tuberculosis in some form was a contributory cause is higher than has usually been assumed, being now shown to have been one in 357 deaths from cancer during 1925 in the mortality experience of the United States registration area.

TUBERCULOSIS AMONG THE AMERICAN INDIANS[1]

STEPHEN J. MAHER

Dr. Benjamin Rush of Philadelphia, popular in his day as a physician and as a statesman, a friend of Washington and Jefferson, wrote a book in the last years of the 17th century entitled *Free Thoughts upon the Cause and Cure of Consumption* (1). One of these "free thoughts" he phrased as follows: "I shall begin my observations upon the consumption by remarking that it is unknown among the Indians of North America."

This "free thought," important if true, was also important though not true. Uttered by so influential a doctor and writer as Rush, it was accepted as truth by many of the authorities and near-authorities, who during the next hundred years spoke or wrote on the subject of tuberculosis among the Indians. And their writings have had much to do with the rather widespread belief that tuberculosis is a disease of Caucasian civilization and that its occurrence among primitive races is one of the penalties these races have paid for contact with the white race.

It is true that most of the accounts by the first European visitors to primitive races of the world fail to make mention of the finding of cases of consumption among the aborigenees. That, however, gives little support to the theory that there were not cases of tuberculosis among these aborigenees. When European visitors, three or four hundred years ago, to whom tuberculosis was a commonplace at home, found tuberculosis a commonplace among strange tribes, they felt, as a rule, no compulsion to record such findings. On the contrary, if they had found no tuberculosis among the newly discovered tribes, there would have been an immediate urge, even among illiterate pioneers, to make this fact known to the world. It is the unusual, not the usual, that is ordinarily considered worthy of record. Nevertheless, if the good Dr. Rush had taken pains to ascertain the facts in the matter, before having "free thoughts" about it, he would have learned that not only was consumption known among the Indians of North America at the time of his writ-

[1] Read at the Fourteenth Annual Conference of the British National Association for the Prevention of Tuberculosis during a Discussion of the Question, "The Occurrence of Tuberculosis among Primitive Peoples," October 15, 1928.

ing, but that it had been known, superficially studied, and repeatedly recorded by certain of the more acute explorers during the one hundred and seventy years before the time of his writing; and also that there was very good reason for believing that tuberculosis in one form or another had always been a disease of the Indians of North America.

As far back as 1633–1634, in the *Jesuit Relations* (2) Le Jeune says that nearly all of the young Indians were attacked by scrofula "both on account of their filthy habits and because they eat and drink indiscriminately with the sick."

Again in 1655, Father Le Mercier (3) reported a terrible case of scrofula in a boy, and a case of haemorrhagic consumption in a girl of the same family of Algonquin Indians. In 1657 the *Jesuit Relations* (4) tell of a full-blooded Huron girl sick with consumption. In 1672 the *Jesuit Relations* (5) describe a case of consumption of two years' duration in an Indian woman.

In the same years Josselyn (6) reported that consumption was one of the chief afflictions of the Indians of New England. La Hontan (7) reported that during his visits to the Indians of Canada from 1683 to 1694 he found them frequently afflicted with "that languishing disorder which we call a consumption. They look pale, livid, and ghastly, like skeletons."

In the first *Massachusetts Historical Collections* are some interesting references to this subject. Daniel Gookin (8), himself one of the earlier settlers of New England, says in his *Historical Collections of the Indians of New England*

> Of this disease of the consumption sundry of those Indian youths died that were bred up to school among the English. The truth is, this disease is frequent among the Indians; and sundry die of it that live not with the English. A hectic fever issuing in a consumption is a common and mortal disease among them. (*Collections of the Massachusetts Historical Society*, i, p. 173.)

On page 140 of the same volume an Indian authority (9) is given for the following statement: "Before the English came among the Indians, there were two disorders from which they most generally died, viz., the consumption and the yellow fever."

In volume 5 of the *Massachusetts Historical Collections* General Lincoln (10) says in *Observations of the Indians of North America*, "Their tender lungs are greatly affected by colds which bring on consumptive habits, from which disorder, if my information is right, a large proportion of them die."

Francis, in his *Life of John Eliot* (11), the Apostle of the Indians, gives as his own opinion, "Consumption seems to have been a common malady among the New England natives."

De Forest on page 20 of his *History of the Indians of Connecticut* (12) says, "The diseases of the Indians were quinsies, pleurisies, rheumatisms, quick consumption, and such others as would be naturally produced by their exposure and hardships, and by their irregular mode of life."

In a notable series of papers in the *Medical Record* in August and September, 1892, on *Diseases among Indians*, Dr. A. S. Holder (13), at one time Agency Physician at the Crow Reservation in Montana, says

> I do not believe that at any time in their history they [the Indians of North America] have been free from consumption and scrofula. In the Peabody Museum (specimen 17, 223) is a part of a vertebral column badly affected with caries-tuberculous, among prehistoric Indian remains. (See illustration in *Orthopedic Surgery*, by Bradford and Lovett, p. 2.)
>
> Tuberculosis is coextensive with the Indian race. The single tribe that may be said to be free from this disease, I have been unable to find after diligent search. Those who inhabit the torrid swamp of Arizona, and those in the frozen northwest territory of Canada, along the western seaboard and in the Atlantic States, all tribes suffer more or less from consumption and scrofula.

Addison (14), in the *Canadian Journal of Medicine and Surgery* for May, 1902, tells of finding in an ossuary near Big Bay Point in Simcoe County, Ontario, several skeletons of Huron Indians that had suffered from Pott's Disease. These skeletons had been under ground for more than two centuries. He concludes that these bones are proof that not only the Indians suffered from tuberculosis before the European invasion, but also that it was a very common disease among them before the white man came.

About 1840 there began to appear in the medical writings of the time a new interest in the occurrence of tuberculosis among the Indians. The opinions expressed by these authors, pro and con, of the question as to whether or not the Indians had tuberculosis before the white man came, are not of great importance, but they show a general agreement that at that time the Indians suffered severely from tuberculosis.

Perhaps one of the most interesting of these writers was Thomas S. Williamson, a medical missioner to the Sioux Indians of Dakota from 1835 to 1846. It was during these years that, because of the encroachments of the white settlers and the destruction of their large game, the Sioux were beginning to change their diet and habits of life. He says (15)

Of those [Indians] over 10 years of age who died of disease (violent deaths were the most common in those wild days), I think fully one-half died of consumption (phthisis pulmonalis). . . . Among the women and children who remained in the neighborhood during the winter, scrofula was almost universal, caused by their subsisting entirely on corn for weeks, and, in some years, for months. Enormous swellings formed about their necks and armpits, and occasionally on other parts of the body, forming abscesses which sometimes so exhausted the system as to prove directly fatal, but more frequently by inducing phthisis or mesenteric diarrhoea. In the spring when the ducks returned, so that they could get animal food, most of them got better and some entirely recovered.

One other writer who makes important observations is Dr. James Walker, Agency Physician, United States Indian Agency, Pine Ridge, South Dakota (16). He says

Tuberculosis existed among these Indians before they came into contact with the white people. At that time the disease was rare among them, and remained so until they changed their nomadic to a settled life in houses.

When they began to live in houses, tuberculosis began to increase among them.

They were filthy, both when they lived in tepees and when they lived in houses. . . .

In this primitive life the principal food of these Indians was flesh. Sometimes they had this in abundance and sometimes they had little. In times of plenty, they would surfeit upon raw or poorly cooked meat, and in times of scarcity, they would go hungry. They had no meal times, but ate when inclined, or opportunity offered. Notwithstanding this unsanitary way of eating, they were comparatively free from tuberculosis.

When they began to live in houses, the Government supplied them with an abundance of food, and in much greater variety than they had been accustomed to. It also supplied them with cooking stoves and utensils so that their food was better cooked than it was when they lived in tepees. Coincident with this increase of food, prepared and taken in a sanitary way, were the increases of tuberculosis among them. . . . From time immemorial, there were a few cases of tuberculosis among these Indians.

For some of the references used in this discussion, I am indebted to an out-of-print report on *Tuberculosis among the North American Indians* prepared by a committee of The National Tuberculosis Association and published by the Government Printing Office in 1923. For others I have drawn on a paper of my own that I wrote twenty years ago. I am

glad of the opportunity to contend before this distinguished assembly that the American Indians, even in the wild, suffered from tuberculosis, and that the doctrine that tuberculosis is a curse that the white race has passed along to the other races of the world is a false doctrine.

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AN ANALYSIS OF 1,000 DEATHS FROM PULMONARY TUBERCULOSIS AMONG INSURED POLICY-HOLDERS

L. H. LEE[1]

The material for this study was taken from the files of the Pacific Mutual Life Insurance Company of California. The data compiled represent the findings on the Medical Examiner's report at the time insurance was issued, the Disability Claim file and the Death Record. A fifteen-year period of time is covered, extending from 1913 to 1928.

It seems reasonable to assume that factors markedly influencing mortality in pulmonary tuberculosis should manifest themselves in the histories of cases actually developing and dying of the disease. Furthermore, these histories should in some degree indicate whether or not underwriting principles operated as expected.

SUMMARY

1: The average time elapsed from the date of application to beginning of illness was 4 years.

2: The average duration of disability was 2 years and 3 months.

3: The average policy life was between 7 and 8 years. For one-third of the policies it was 5 years or less; for one-third, 5 to 10 years; and for one-third, over 10 years.

4: The average age at the time of application was 32 years.

5: The average age at the beginning of illness was approximately 35 years.

6: The average death-age was between 38 and 40 years.

7: 761 cases were underweight, as follows: 200 were 5 per cent, 246 were 10 per cent, 188 were 15 per cent, and 127 were 20 per cent and more underweight; while 239 cases were overweight.

8: There was a family history of tuberculosis in 7.4 per cent of the underweights and 8.7 per cent of the overweights.

[1] Pacific Mutual Life Insurance Company of California, Dr. W. W. Beckett, Medical Director, Los Angeles, California.

9: Low blood-pressure (systolic under 110 mm.) was found in 3.2 per cent of the underweights and 2.1 per cent of the overweights.

10: A history of influenza was found in 11 per cent of the underweights and 5.9 per cent of the overweights; and a history of common colds in 5.4 per cent of the underweights and 6.2 per cent of the overweights.

11: A history of lymph-node enlargement was found in only 2 cases.

12: Such factors, as a history of haemoptysis, pleurisy, empyema, tuberculosis, or change for health, do not show in a marked degree because they have been removed by selection. The weight of their influence can only be determined by a study of substandard experience.

CONCLUSIONS

1. Underweight is the factor which most clearly indicates a bad prognosis.
2. A family history of tuberculosis associated with underweight is of less importance than is generally assumed. This conclusion is drawn from the fact that there was a positive family history in just as high a percentage of overweights as in underweights.
3. A personal history of upper respiratory disease is a common finding and of importance, especially if the condition is chronic or recurrent.
4. Low blood-pressure is not of vital prognostic significance.
5. This study indicates one deviation from present standards. More attention should be given to underweight *per se*, and more favorable action is indicated in dealing with a family history of tuberculosis.

The fact should be kept in mind that death-claims represent only a certain portion of lives exposed over a given period of time. For that reason one must guard against "snap-shot" faulty deductions.

The purpose of selection is to avoid disability and death-claims which occur more frequently or in less time than is naturally expected. A study of claims arising from any disease such as tuberculosis is of value in that it brings to light factors which were favorable for the production of disability and death from that disease in spite of good selection.

THE EXPERIENCE OF PHILADELPHIA'S TUBERCULOSIS PATIENTS IN CLINICS AND STATE SANATORIA

DOROTHY E. WIESNER AND LUELLA H. SMITH[1]

The experience of a tuberculosis patient who is cared for by the public begins in the clinic to which he may have been sent by his personal physician, or by a social agency, or may have gone of his own accord for examination. There he is placed on the list for admission to a state sanatorium. After a delay, during which he remains under the clinic's supervision, he goes to the state sanatorium for treatment. Here he remains until such time as he has learned to care for himself properly, perhaps with his disease arrested, or is released by death, or may take into his own hands the matter of leaving. From the sanatorium he is referred again to the local clinic from which he set out, which has kept his family under supervision during his absence and prepared the way for his return. From this clinic more than one in ten again begins the same round of being listed, going to the sanatorium for treatment and of return again to the clinic.

During the past few months the Philadelphia Health Council and Tuberculosis Committee has made a study of the experience of such tuberculosis patients referred to state sanatoria from Philadelphia clinics. Records of patients sent from 5 clinics were studied. These were the Henry Phipps Institute, the Jefferson Hospital Chest Department, the Kensington Dispensary, and the Negro Health Clinics nos. 3 and 4 of the Health Council. The study was made possible by the interested coöperation of the physicians, nurses and other workers at the clinics mentioned and at the Department of Public Health, which made its records available. It includes the history of patients listed for sanatorium care in the four years 1924–1927 from these clinics.

The object of the study was to find out what the results of the clinic and sanatorium services were in a group of patients, and also, by following them step by step from the clinic to the sanatorium and back to the clinic again after discharge, to observe the workings of the machinery for handling tuberculosis patients in the city and state.

[1] Philadelphia Health Council and Tuberculosis Committee, Statistics and Research Service, Philadelphia, Pennsylvania.

Confining itself to the patients listed by the clinics for state sanatoria, the study did not of course include all of the patients served by the tuberculosis clinics but only this small percentage of them. Nor did it include all of the clinics of the city.

The study included a total of 884 patients, which is about one-fourth of the total number listed for the state sanatoria by all Philadelphia clinics during these four years. It approximates the number listed for the state sanatoria from all Philadelphia clinics in a single year. It is believed that this number is adequate to give a general picture of Philadelphia patients referred to the state sanatoria.

I

Let us look at the first clinic experience. During the four years, 1924–1927, there were about 14,000 patients registered at the clinics mentioned, of whom 30 per cent, or 4,200, were diagnosed as tuberculosis cases. Of this number 884 were listed for state-sanatorium treatment, from which it appears that about one-fifth of the diagnosed tuberculosis cases in Philadelphia clinics are listed for state-sanatorium treatment.

Of the 884 patients who were placed on the list for the state sanatoria, 655, or 74 per cent, actually went to these institutions. Two hundred and twenty-nine, or 26 per cent, did not go when the opportunity came. The reasons why they did not go were in many cases those connected with home situations, such as parents being unwilling for their children to leave home, or one of the parents fearing that the family would suffer or be broken up in his absence. A number of patients entered some other sanatorium than a state institution, some left town before the appointment came, going to relatives in other localities, some were too ill to go when the appointment came, some had improved in health and were unwilling to go, and some refused to leave their jobs. Ten died before the appointment came.

When a comparison is made of the persons listed for the sanatoria and those who accepted the treatment, it appears that the age-group which was most apt to accept the appointment after being placed on the list was that from 15 to 19 years, the time when there are fewer economic and domestic problems influencing the individual. The ones least likely to accept the appointment were in the ages 35 to 49, which might be expected, as these are the years of the greatest economic and social responsibilities. Men were more apt to accept the appointment than women.

probably because the man can leave with less injury to the home than can the housewife. In the group from 35 to 49 years of age it was the women who refused most frequently. Of the men in this age group 76 per cent actually went to the sanatorium, but of the women only 49 per cent accepted the appointment.

Of those on the admission list for the state sanatoria, 115, or 13 per cent, were Negroes and of those only 64, a little more than half, went to the sanatorium. Evidently Negroes are less likely to accept sanatorium care than are the Whites.

The 655 persons who finally went to the state sanatoria from these clinics included persons in various stages of the disease. Clinics attempt to find early cases by examining contacts and keeping them under super-

TABLE 1

Length of sanatorium treatment according to condition on admission

PATIENTS ACCORDING TO CONDITION ON ADMISSION	TOTAL	PATIENTS ACCORDING TO NUMBER OF DAYS IN SANATORIA					
		1–29	30–89	90–179	180–364	365 and over	Still in sanatorium
Total	655	51	164	141	151	59	89
Nontuberculous	46	1	26	5	5	3	6
Latent	60	1	24	17	16	0	2
Minimal	105	2	32	29	19	6	17
Advanced	191	24	37	36	49	18	27
Far advanced	253	23	45	54	62	32	37

vision, and obviously the earlier the stage of the disease in the patient the more probable his recovery. It is interesting to note, then, that out of 655 persons sent to the state sanatoria 105 only, or 16 per cent, were minimal (early) cases, 191, or 29 per cent, were advanced and 253, or 39 per cent, were far advanced, 9 per cent were latent and 7 per cent nontuberculous. It should be kept in mind that the small number of early cases sent to state sanatoria does not include all of the tuberculosis patients diagnosed as "early" at these clinics but only those who for economic or other reasons were listed for admission to the state institutions.

The large number of advanced and far-advanced cases, 68 per cent, sent to the state sanatoria, indicates that special stress is placed upon the removal of infectious cases from their home environment in order to

prevent the spread of the disease to others. Had it not been so necessary to isolate the large number of advanced cases or had there been provision in the city itself for the care of such cases, undoubtedly more early cases would have been listed for the state sanatoria.

Those who finally went to the state sanatoria did so after being obliged to wait various lengths of time before being called. The shortest period was 5 days and the longest nearly 8 months. The waiting list for the state sanatoria varied from 400 to 1100 names in 1927. The average number of days on the waiting list for the patients who went to the sanatoria was 46 days, just over a month and a half. Forty per cent of them were admitted within a month, 36 per cent within the second month, 10 per cent within the third month, 6 per cent within the fourth month,

TABLE 2

Patients discharged according to condition on discharge and number of days between discharge and first clinic visit

CONDITION ON DISCHARGE	TOTAL PATIENTS	NUMBER OF DAYS BETWEEN DISCHARGE AND FIRST CLINIC VISIT					
		1–29	30–89	90–179	180 and over	No visit	Unknown
Total patients	506	207	77	22	30	159	11
Arrested	54	28	6	2	2	15	1
Quiescent	44	15	10	2	3	13	1
Improved	298	134	51	14	21	72	6
Unimproved	107	30	10	3	4	57	3
No record	3	0	0	1	0	2	0

4 per cent within the fifth month, and 2 per cent had to wait 6 months or more.

A number of those going to the sanatoria had been placed on the waiting list more than once; in fact the 884 patients showed a total of 1,042 listings. Ninety-eight persons had been placed on the list for admission twice, 18 three times, and 8 four times during the years studied.

Some went directly from work to the sanatoria. Of those admitted to the sanatoria during these four years, 212, or 32 per cent, lost no time from work before admission. Those who did lose time from work lost, for the most part, from 2 to 5 months, but 75 persons were unable to work for more than a year. It should be mentioned that of the 212 who lost no time from work more than one-half were children under 15 years of age. Of the adults 20 per cent lost no time from work before sanatorium

treatment. Of the women 34 per cent lost no time from work prior to treatment. This is largely due to the fact that a person doing housework was classified as a person working and such women should probably not have been carrying home responsibilities at this time.

II

The next phase of the history of these patients is that of their sanatorium care. It appears that of the 655 of this group received at the sanatorium, the largest number, 164, stayed at the sanatorium for from 2 to 3 months, 51 left before the end of the first month, and 59 stayed

TABLE 3

Summary of subsequent medical experience of discharged patients

CLASSIFICATION ON DISCHARGE	TOTAL PATIENTS	SUBSEQUENT MEDICAL SUPERVISION			
		Hospital or sanatorium care*	Clinic but no hospital or sanatorium†	Private physician	None or no record
Total patients	506	144‡	239	31	92
Arrested and apparently arrested	54	10	31	1	12
Quiescent	44	9	22	1	12
Improved	298	88	150	18	42
Unimproved	107	36	35	11	25
No record	3	1	1	0	1

* Includes 23 patients in hospitals for causes other than tuberculosis.

† Includes all patients who returned to any clinic after sanatorium.

‡ Of these 144 patients, 125 also returned to clinic.

more than a year. The average time stayed by those in this group was 184 days, or a little more than 6 months.

It was noticeable that only 5 per cent of the women, as compared with 9 per cent of the men, left within one month after admission. Apparently it is true that when arrangements are finally made for a woman to go to the sanatorium there is less prospect of her giving up and returning home without making an adequate effort to recover. However, the average length of stay for women was slightly less than for men, being 171 days for women as compared with 188 days for men.

When the length of treatment in the sanatorium is considered for the various ages it appears that the years of an individual's life when economic strain is least severe are those in which the stay at the sanatorium

is likely to be longest. Persons from 15 to 19 years of age stayed 234 days on the average and persons 50 years old and over, 201 days. These are the years in which economic strain would ordinarily be least. The shortest stay was for those aged 35 to 49 years, an average of 158 days; those from 20 to 34 years old averaged 184 days of treatment, and children under 15, many of whom were at the summer preventorium, averaged 164 days.

When the length of stay in the sanatorium and the condition on admission are correlated it appears that of the 51 persons who stayed less than a month, 24 were advanced and 23 far advanced on admission. Many of these doubtless were too sick to benefit by sanatorium treatment

TABLE 4

Condition of patients on January 1, 1928, according to year of discharge

YEAR OF DISCHARGE*	TOTAL PATIENTS	KNOWN TO BE LIVING						DIED AFTER DISCHARGE		NO INFORMATION AS TO LIVING OR DEAD	
		Total living		Working†		Not working					
		Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Total patients.....	506	290	57	168	33	122	24	69	14	147	29
1927.....	174	132	76	68	39	64	37	10	6	32	18
1926.....	161	89	55	58	36	31	19	21	13	51	32
1925.....	117	57	49	37	32	20	17	24	20	36	31
1924.....	54	12	22	5	9	7	13	14	26	28	52

* Where more than one discharge occurred to a patient, the date of the first is considered.
† "Working" includes housework and school attendance.

and returned home to die. It should have been possible for such patients to receive treatment nearer home where their friends could visit them frequently and they could keep in touch with family life.

As might have been expected, 50 of the 59 persons who were in the sanatorium over a year were advanced or far advanced upon admission. The latent and nontuberculous cases were likely to stay 2 or 3 months only.

When the patients were discharged from the sanatorium, 8 per cent of the 655 were discharged as *arrested* or *apparently arrested*, 7 per cent as *quiescent*. The most frequent classification was *improved*, which characterizes 45 per cent of the whole number admitted. Sixteen per cent were discharged *unimproved* and 9 per cent died at the sanatorium.

Of the 54 patients who were discharged as *arrested* or *apparently arrested*, none left the institution until he had had at least 3 months' treatment. Twelve had from 4 to 6 months' and 32 from 7 to 12 months' treatment. Ten stayed more than a year.

In addition to the classification given on the sanatorium discharge card as to the physical condition of the patient, the card also indicates whether the patient left with consent or against advice of the sanatorium physician. Less than half of those discharged in these 4 years from the sanatoria left "with consent," 242, or 48 per cent, left "against advice," and 24 were dismissed for bad conduct.

TABLE 5

Patients admitted to sanatoria according to sputum reports and condition on January 1, 1928

CONDITION ON JANUARY 1, 1928	TOTAL PATIENTS	SPUTUM REPORTS		
		Positive*	Always negative	No sputum reports
Total patients	655	308	182	165
No recurrence	108	15	32	61
Occasional sickness	99	39	40	20
Usually sick	53	29	13	11
In sanatorium or hospital	119	59	28	32
Dead	129	109	10	10
No record	147	57	59	31

* Includes all patients whose sputum was positive at any time during clinic attendance.

III

This brings us to the consideration of this group after discharge.

Persons discharged from the sanatorium are referred again to the local clinic from which they came. This was done with the entire 506 persons who were discharged. The notification of discharge is sent to the Philadelphia Department of Public Health and from that office to the local clinic. The date of receipt of this notification is recorded, and a study of these dates shows that 130 of these notices were received at the clinic within a week from discharge and 243 more within 4 weeks. Eleven were delayed and came in late, 4 or more weeks after discharge. For 122 the date of receiving the notices could not be determined. This record of transfer back to the clinic is excellent.

Just as there is comparatively little time between discharges from the

sanatorium and receipt of notices at the clinic, so the time between the discharge and the first visit of the patient to the clinic after he returns home is short. Of the discharged patients 207, or 41 per cent, presented themselves at the clinic within a month after their discharge from the sanatorium. There were 20 per cent who came 2 to 6 months after discharge and 6 per cent who came after 6 months. Two-thirds of the discharged patients were under the supervision of the same clinic from which they had been sent to the sanatorium and most of them within a month.

Of the one-third of discharged patients who did not report to the same clinics, 57 were unimproved. It was found that a number of these returned from the sanatorium either to die in their homes or in local hospitals within a few weeks. Some had changed their home addresses and had gone to other clinics, still others returned to the care of private physicians, being patients referred originally by the private physician to the clinic for sanatorium listing. In all but a few cases there was a valid reason for failure to return to the clinic.

In addition to the two-thirds of the discharged patients who were under supervision at the same clinic, there were 28 who were known to be under supervision at other clinics. Thus a total of 364, or 72 per cent, of the patients discharged from the state sanatoria came under clinic supervision, more than half of them within one month after discharge. This is a most encouraging situation.

An inquiry as to the time which elapses after the discharge of the patient before the first visit of the nurse to the home indicates that 39 per cent were visited by the nurse during the first month after discharge, 15 in the second and third months, and 6 in the fourth, fifth and sixth months after discharge. One hundred and sixty-three were never visited, and there were a few for whom the date of the first visit was not available. In some cases the nurse learned that the patient was attending another clinic, was at the Philadelphia General Hospital or another hospital, or was under the care of a private physician.

It is an interesting fact that more than one-fourth of the patients discharged from the state sanatoria during the 4 years returned at some time to institutional care either at the state sanatoria or elsewhere, the actual number being 144, or 28 per cent. It was, as might have been expected, the unimproved patients who were more likely to resort again to institutional care, 34 per cent of the unimproved cases doing so, whereas only 30 per cent of the improved, 20 per cent of the quiescent and 19 per cent of the arrested did so.

IV

What was the condition of the patients discharged in these four years on January 1, 1928? No attempt was made to follow up the patients in their homes but this information was secured from the clinic records. Of the discharged patients this information showed that 290, or 57 per cent, of those discharged were known to be living and 69, or 14 per cent, had died after discharge.

The condition of those discharged may be considered both from the standpoint of their ability to work and from the standpoint of their subsequent experience with tuberculosis.

When considered as to their ability to work, it was found that 168, or 33 per cent, of those discharged were working on January 1, 1928; 122, or 24 per cent, were not working; 147, or 29 per cent, were unknown; and 69, or 14 per cent, had died since leaving the sanatorium.

In view of the efforts being made to find suitable work for persons with arrested tuberculosis, information was secured regarding the subsequent working capacity of this group as to how many at any time in the four years returned to former occupations, entered new occupations, and how many never worked after discharge. Of the 506 patients discharged, 147 returned at some time to their former occupations; 96 of these were students at school, 11 mothers returning to their homes, and 40 persons returning to previous remunerative occupations. New occupations were undertaken by 60. There were 16 who worked, but occupation was not stated. There were 138, or 27 per cent, who never worked after their discharge from the sanatorium. Thus 223 of the 506 discharged persons, or 44 per cent, took up either their previous activities or engaged in new work at some time after their discharge from the sanatorium, 116 of these in remunerative work. At least one-third of all those discharged were known to be actually at work on January 1, 1928.

When those discharged are reviewed as to the condition of their health on January 1, 1928, it is found that 21 per cent were well, that is, without recurrence of their tuberculosis; 20 per cent had had occasional relapses; 10 per cent were usually sick; 6 per cent had returned to the sanatorium for further treatment; and 14 per cent had died since leaving the sanatorium. Regarding the other 29 per cent, there was no information available.

Because of the importance of positive sputum in the diagnosis and outcome of tuberculosis, the condition of the patients on January 1, 1928, was correlated with the facts concerning sputum reports. Of the 655

patients admitted to state sanatoria during the four years covered by the study, 47 per cent had positive sputum at some time during clinic attendance, for 28 per cent the sputum reports were always negative, and for the remaining 25 per cent there was no information about sputum reports. When we correlate the condition on January 1, 1928, with these facts concerning sputum reports, we find, as usual, that those who have negative sputum have a much better chance for recovery. Of the 129 patients who died, all but 20 had positive sputum. On the other hand, only 15 of the 108 classified "no recurrence" had positive sputum.

Information concerning the family income at the beginning of this year was available for many of these families. These figures included the wages for all members of the family, regular assistance from relatives and relief from social agencies. An income of less than $5.00 per week for each member of the family appeared to have been most common, that is, families of 5 had less than $25.00 per week. Fifty-eight of those from whom information was available had such an income. Fifty-three families had from $5.00 to $9.00 per week for each member of the family, and 13 had from $10.00 to $14.00 per week for each member. Eight had $15.00 or more per week for each member.

The tuberculosis nurse keeps the family under supervision while the patient is at the sanatorium. She frequently visits the home and tries to adapt it for the return of the patient after his discharge.

In some instances the nurse had been able to secure improvements in housing conditions, sometimes even moving the family. From the records it is possible to state that for 55 of the 260 persons whom the clinic nurses were supervising on January 1 the housing conditions were better than before the sanatorium experience. In 142 cases the housing conditions were not altered and in 63 there was no record regarding this matter.

As regards the sleeping accommodations, information concerning 260 of the discharged patients who were under clinic supervision at the first of the year shows that there was a separate bedroom for only 79 of these patients. Twenty-eight others shared a bedroom but had a bed to themselves. The greater number, 119, did not have a separate bed. Of these 119 persons 17 were described as usually sick and 37 as occasionally sick.

V

We have selected three of the individual records which illustrate specific points. The first illustrates the coöperation of social agencies

in a single case. A colored woman of 32 first came to the clinic in May, 1924. Her husband had died of pneumonia three weeks before, leaving her with seven children; the oldest one 11 years of age. The family was in destitute circumstances and the clinic nurses immediately set to work to improve the home conditions, securing support from the Mothers' Assistance Fund. Two years later the patient was found to have positive sputum and was sent to the state sanatorium, a moderately advanced case. A sister cared for the children during her absence, and at the end of three months she was discharged quiescent and able to work. The family moved to better quarters and the patient again returned to the supervision of the clinic. Several months later she was referred to the Placement Bureau of the Philadelphia Health Council with very good references from previous employers. At present she is an arrested case and is caring for her family as well as doing a day's work occasionally to supplement the family income.

Another illustrates a remarkable recovery. A single woman of 28, born in Russia, came to the clinic in August, 1924, and was immediately listed for the state sanatorium as a far-advanced case. She had been employed as a clothing operator but had been unable to work for several months. The appointment for the sanatorium came on October 1st, and before the end of the year the patient was discharged with consent as a quiescent case. She returned very soon to the clinic and is still in attendance there. Since discharge from the sanatorium the patient has married and now has one child. During the past three years she has been remarkably well and has had no recurrence of the disease.

Another is an example of a most difficult case. An Italian, 36 years of age and the father of four children, was listed for the state sanatorium late in 1925. Previous to this time he had been a patient in two local tuberculosis wards but had stayed only a short time in each. When the patient left for the state sanatorium his wife, a mental case, was taken to the Philadelphia Hospital for Mental Diseases, and the children were placed in Catholic homes. During the two years 1926 and 1927 this man was admitted four times to the state sanatorium. Each time he left against advice and never stayed more than three months. He was also admitted three times to local hospitals during these years but was always uncoöperative and refused to stay. When this study closed his diagnosis was far advanced tuberculosis and he was awaiting another appointment to Mt. Alto State Sanatorium.

VI

In following the experience of this group from clinic to sanatorium and back again to the clinic, one cannot but be impressed with the continuous decreases in the numbers of the group and the modest proportion who have finally come back to a normal adjustment in society. This is the tragedy of tuberculosis, a tragedy not only to those who suffer from the disease, but also to their relatives and friends, and to society.

We have seen that, of the number who in the beginning of the study were found in the clinic to need sanatorium care and placed on the list for admission to state institutions, more than two-thirds are in the advanced stages of the disease. After being placed on the admission list they must wait a month and a half on the average before securing treatment. During this time some die, some become too ill to go, some decide to stick to their jobs to the bitter end, others find friends able to take care of them in other places, and some secure admission to other institutions. The number of 884 shrinks to 655 who finally succeed in entering the sanatorium, 26 per cent having dropped out for one reason or another.

At the sanatorium this 655 decreases further because of the death of 60, or 9 per cent, while 89 stayed beyond the period which was studied; so that 506 of the original number are discharged from the sanatorium. And of these it is found at the end of the period that 14 per cent have died, 6 per cent are in a sanatorium for further treatment, 10 per cent are usually sick, 20 per cent are occasionally sick, and 21 per cent are well, although, as stated, at least 33 per cent are able to work. The balance have disappeared from the records.

From the point of view of those who forget the human element and the vast difficulties of persuading tuberculosis patients to follow the pathway most promising for their health, these results will doubtless appear discouraging. But from the standpoint of those who are actually carrying on clinic and sanatorium work and who know the difficulties of the problem, the results will seem most encouraging, since they show so many actually restored to efficiency and readapted to society.

The experience of these patients shows also very clearly that there is in operation in Pennsylvania a system of transfer from clinic to sanatorium and from the sanatorium back to the clinic from which the patient was sent, which is well adapted to meet the needs of tuberculosis patients. That system has been in effect for a number of years, and so far as could be discovered, is peculiar to Pennsylvania. A similar system

exists within the limits of certain cities, notably Chicago, Cleveland, Detroit and Seattle, but these are not of statewide scope.

Finally, this study emphasizes again the need for a tuberculosis hospital in Philadelphia for advanced cases of the disease and for children. Here are two classes of patients who should not usually go far from home for treatment but who especially need to have care.

The long delay which both adults and children undergo after being placed on the waiting list for a state sanatorium, the very large proportion of patients with advanced and far-advanced tuberculosis placed upon that list to the exclusion of early cases, the relatively large number of persons with advanced and far-advanced tuberculosis who after going to the sanatorium return to their homes within a month without having received the full benefits of the care offered: these all stress the need for greater local provision for advanced cases.

Such patients must have hospital care in order to prevent the spread of the disease. They should be cared for near their homes where they can be visited by their friends and can be in touch with the home life. Only so will they be saved from that discontent and homesickness which brings so many from the state sanatoria back to their old environment against the advice of the sanatorium physicians. Probably not all of the 48 per cent who leave the sanatoria against advice would continue under treatment anywhere, but without doubt many of them would do so if they could keep in touch with their homes and friends.

If adequate provision were made in Philadelphia for persons with advanced tuberculosis, longer periods of treatment would be accepted by them, patients with positive sputum would be cared for out of the home for a longer time, and the dangers of spreading infection would be less. The strain on the long waiting list for the state sanatoria would be relieved, delays in securing treatment would be avoided, and our clinics would be able to list a larger number of early cases for the state sanatoria of those who are better able to go away from the city for treatment.

It appears that from whatever angle we study the tuberculosis situation in Philadelphia, the need for more adequate local hospital provision for tuberculosis pushes itself into the foreground.

ACCIDENTAL PNEUMOPERITONEUM AS A COMPLICATION OF ARTIFICIAL PNEUMOTHORAX[1]

LEROY ELRICK

Accidental pneumoperitoneum, which has also been described as subdiaphragmatic emphysema, is a rare complication of artificial-pneumothorax treatment. In a search of the literature available to me in the English and German languages, I was able to find reports of only 11 cases (references (1) to (9)), and possibly one of these should not be classed as pneumoperitoneum (a case of Saugman and Hansen, discussed subsequently). However, I have heard of one or two cases which were not reported, and it would also be an easy matter to overlook a pneumoperitoneum unless it were found by physical examination, X-ray or fluoroscope soon after its occurrence, as the air in the abdomen is absorbed in a few days or a few weeks. Consequently, this complication may be a little more common than a review of the literature would indicate.

The ordinary manner of production of an accidental pneumoperitoneum is through the puncture of the diaphragm with the pneumothorax needle, followed by the direct introduction of air into the peritoneal cavity. Certain authors, however, believe that they did not puncture the diaphragm, but that the air entered the abdomen in some other manner.

For example, in a case reported by Parfitt and Crombie (1), in which a small pneumothorax had already been obtained, they believed that the needle did not puncture the diaphragm,

> as the puncture had been made at the known site of the pocket and the fluctuations of the fluid levels of the manometer had been in proper relation to the respirations. Shortly afterwards the fluctuations were seen to be reversed in phase of respiration; and after running in more gas the patient complained of epigastric discomfort.

Air was then found to have entered the abdomen. The authors describe the complication as an "escape of gas into the peritoneal cavity." As

[1] Read at a meeting of the Denver Sanatorium Association, Denver, Colorado, May 22, 1928.

to the manner in which the escape occurred they do not express an opinion.

Saugman and Hansen (p. 327 and p. 339 (2)) in one case gave the pneumothorax treatments on the left side, and produced a small pneumothorax by the use of high pressures. After the eighth treatment air was found by the X-ray to be present under the diaphragm on the right. They believe that a mediastinal emphysema occurred, and that from the mediastinum the air extended along the aorta into the retroperitoneal tissue and then spread out between the diaphragm and liver, pushing the peritoneum before it. If this explanation is correct, the air remained outside the peritoneum and the term *subdiaphragmatic emphysema* would be more exactly descriptive of the condition than the term *pneumoperitoneum.* The possibility might be worth considering, that the air may have entered the abdominal cavity through a tear in the peritoneum. As to the manner in which the air reached the mediastinum from the pneumothorax pocket, the occurrence of mediastinal emphysema as a complication of artificial pneumothorax and the method of its production have been discussed by a number of writers (1) (p. 326 (2)) (10) (11) (12) (16) (17). According to various opinions expressed by them, the air may be injected into the tissues of the chest-wall just outside the costal pleura, and from there spread within the chest-wall to the mediastinum; or the point of the needle may enter the interstitial tissue of the lung and the air be injected into this tissue, in which it works its way to the root of the lung and enters the mediastinum; or the air may enter the interstitial tissue from the alveoli, following laceration of them by the needle.

In connection with the possibility of air extending from the mediastinum into the abdomen, it is interesting to note that Lorey (18) reports a case in which the opposite thing occurred: that is, the passage of air from the peritoneal cavity upward through the mediastinum into the neck. An artificial pneumoperitoneum had been performed for diagnostic purposes. When the patient stood up to have an X-ray taken she suddenly became extremely dyspnoeic, and subcutaneous emphysema appeared above both clavicles, without being present anywhere else on the body. Evidently there had occurred a tear of the peritoneum, through which the air passed into the connective tissue surrounding the oesophagus, thence up through the aortic or oesophageal opening of the diaphragm into the posterior mediastinum, and from there into the neck.

In rare instances, due to a congenital defect in the formation of the diaphragm, there is direct communication between the pleural and peritoneal cavities (19) (20). In such a case, which our experience with artificial pneumothorax teaches us must be very uncommon, there could be direct passage of air from the pleural to the peritoneal cavity.

In some of the reported cases of pneumoperitoneum complicating artificial pneumothorax the accident occurred after a pneumothorax pocket had been obtained; in others no free space had been found. The cause of the accident in some cases was an abnormally high diaphragm, either as a result of contraction of fibrous tissue in the lung, or, in one case (3), as a result of a phrenic-nerve exairesis.

Most authors do not give the intraäbdominal manometer readings. In Zink's second case, however (p. 169 (4)), the initial reading, with the needle in the peritoneal cavity, was −7, −8 cm. of water. After the injection of 300 cc. of nitrogen the reading was −2, −1. In Gerber's case (8) the initial reading at the operation at which the pneumoperitoneum occurred was −5, −10. The pressure rose slowly until 400 cc. of air had been introduced, the final pressure being 0, +3. Paradoxical manometric fluctuations were not noticed in these cases. In Rosenblatt's case (9) the initial intraäbdominal pressure was −3, −2 cm. of water, which rose after the injection of 500 cc. of air to −1 to 0. During the operation it was not noticed whether the fluctuations were reversed or not, but after the pneumoperitoneum was discovered by X-ray, a needle was again inserted in the same place and reversed readings were found to be present.

No harmful result from the complication was reported in any case.

The case to be reported is that of a woman 31 years old, with pulmonary tuberculosis of about five years' duration. During this time she has had cough, expectoration, and occasional fever and right-sided pleurisy. Four years ago she is said to have had a pleural effusion on the right. The sputum has shown tubercle bacilli at several examinations. The patient has been in bed for about two years.

When examined in April, 1928, the right lung showed signs of cavitation over the upper two-thirds, with medium to coarse râles throughout. The base was flat to percussion, with very distant breath-sounds.

The left lung showed a few fine râles on cough in the second interspace and at the base anteriorly.

To X-ray the right side was so opaque, especially in the lower part, that nothing very definite could be told about the condition of the lung. The

position of the diaphragm could not be determined. The trachea and heart were pulled to the right (figure 1).

On account of the flatness on percussion at the right base it was thought that there might be a pleural effusion, in spite of the fact that the heart was displaced toward that side. Exploratory puncture, however, did not reveal any fluid.

Though it was probable that the pleura was adherent, an attempt at artificial pneumothorax on the right side seemed indicated. At each treatment only small fluctuations of the manometer were obtained, around the zero point or slightly negative to start with, and only 50 to 150 cc. of air could be introduced, this amount raising the pressure to anywhere from a +2 to a +8 cm. of water, with a variation of 1 or 2 cm. (Pressure values were read as the fluctuation of the fluid level from the zero mark in one limb of the manometer only, instead of taking the difference between the levels of fluid in the two limbs of the manometer. Consequently the readings given represent but half of the true pressure.) Punctures were made at various locations around the base and as high up as the second interspace anteriorly.

At the second treatment the site chosen was in the eighth interspace in the posterior axillary line. The manometric readings on this occasion were reversed, becoming more positive on inspiration and more negative on expiration. The first reading was expiration 0, inspiration +1, and after introducing 25 cc. of air the reading was expiration +2, inspiration +3. The patient complained of pain in the abdomen, and the needle was withdrawn. The possibility that the diaphragm had been punctured was considered.

Much reliance in diagnosing this complication cannot, however, be placed on the character of the manometric readings. Reversed or paradoxical manometric fluctuations occasionally occur as a result of paradoxical movements of the diaphragm, in cases of pneumothorax with positive pressures, and less often with negative pressures, and do not necessarily mean puncture of the diaphragm (p. 321 (2)) (p. 368 (13)) (p. 183 (14)); and, on the other hand, cases of puncture of the diaphragm have been reported without reversed fluctuations being noticed (p. 169 (4)). Unless paradoxical readings were being watched for, however, their occurrence might easily be overlooked. In regard to this complication Riviere (15) says, "Puncture of the abdominal cavity through an unexpectedly high diaphragm . . . . shows a negative pressure with reversed respiratory fluctuations. In some cases, however, the fluctuations are said to follow the normal type at first, and only become paradoxical after some gas has been allowed to enter."

At the next treatment there was pain in the abdomen and neck. Following this, and three days after the operation at which the paradoxical readings had been noticed, an X-ray was taken (figure 2). It showed a small pneumothorax, but no air under the diaphragm. Evidently the reversed fluctuations at the

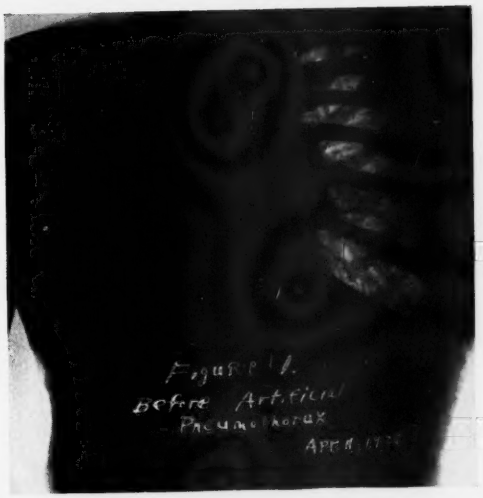
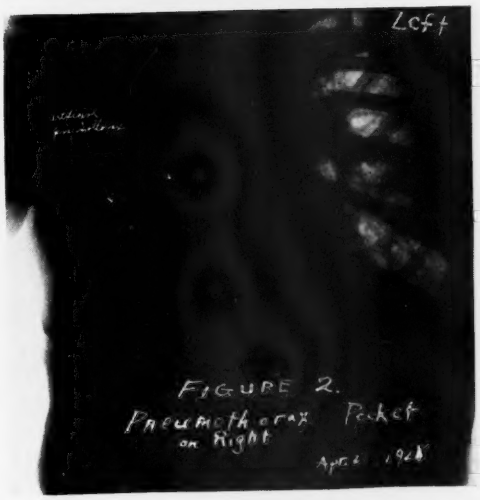


Figure 1.
before Artificial
Pneumothorax


Left
FIGURE 2.
Pneumothorax Pocket
on Right
April 1928

Left
Pneumothorax
Diaphragm
Pneumoperitoneum
FIGURE 3
May 12, 1928

second treatment had been due either to paradoxical movements of the diaphragm, or to the insufflation into the abdomen of a small amount of air, which had been absorbed before the X-ray was taken. Which of these two things occurred, it is impossible to say. Since the production of a small pneumothorax, the diaphragm had now become visible, and was seen to be pulled up much above its normal position. The flatness to percussion at the base had been due to the high position of the diaphragm.

As the patient had felt much better since pneumothorax was instituted, it was decided to continue it for a while and attempt to enlarge the pocket that had been obtained.

Up to this point a blunt needle had been used, as less apt to wound the lung, but at subsequent operations a sharp-pointed needle was employed, as a pneumothorax pocket was now known to be present, and no difficulty in entering this pocket was anticipated.

During the seventh treatment the patient began to have a very severe pain in the region of the right apex. On this occasion the initial pressure was inspiration −1 cm., expiration 0. One hundred cubic centimetres of air were introduced, stopping with a pressure of +8 cm. on inspiration, +9 cm. on expiration. The pain lasted several days. Three days after this operation another X-ray was taken, and this showed air under the right half of the diaphragm (figure 3). The pneumoperitoneum does not show very plainly in a small reduction, but in the original X-ray film the diaphragm is seen to be separated from the liver by a layer of air. The reversed manometric fluctuations had not been noticed during any of the treatments since the previous X-ray, but may have occurred and have escaped observation, as the oscillations were so small and irregular. Therefore it is not certain at what operation the air entered the peritoneal cavity, though probably at the seventh.

Subcutaneous emphysema had been present after some of the treatments and had extended as high as the neck.

The possibility of puncturing the diaphragm is ordinarily negligible when giving artificial pneumothorax, especially when a pocket of air in the pleural cavity has already been obtained. But in this case the diaphragm was much higher than normal. The pleura was also greatly thickened and, in the absence of good manometric readings, it was difficult to tell when it had been completely traversed by the needle. The result was, apparently, that the needle was pushed on through the diaphragm.

The patient suffered no bad effects from the complication. Pneumothorax was soon afterward discontinued, when it became certain that an effective collapse could not be obtained; and the first stage of a thoracoplasty was recently performed by Dr. W. H. Thearle.

In connection with this subject the question arises, whether the diaphragm might be punctured during an exploratory paracentesis for fluid in the pleural cavity in such a case as this, with a high diaphragm, the position of which is not shown by the X-ray. Under these circumstances it would seem to be an easy matter for such an accident to occur, as during the paracentesis the operator would not have even the help of a manometer in determining the location of the needle-point.

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THE USE OF IODIZED OIL IN PULMONARY TUBERCULOSIS[1]

EVERETT K. GEER, F. F. CALLAHAN AND D. GRETH GARDINER

It is intended in this paper to give our personal experiences with iodized oil used in tuberculosis patients rather than an exhaustive review of the literature.

It is well established that in nontuberculous diseases of the chest, notably bronchiectasis and to a lesser degree lung abscess and empyema, the use of iodized oil has been a very real contribution toward more exact diagnosis. For tuberculosis patients there has been marked reluctance in using it. Active pulmonary tuberculosis is mentioned quite consistently in the literature as contraindicating intratracheal injections of iodized oil, and this we have rigidly observed. However, we have been unable to find any well-proved reasons for this attitude. The objection to iodine and iodides for tuberculosis is, after all, an empirical one with little or no experimental evidence to substantiate it. The objection to the introduction of a foreign substance into the bronchial tree in the presence of an acute infection appears more valid, and particularly when this substance scatters throughout the lungs as iodized oil does with cough.

It seems to us, after carefully reviewing the accounts in the literature of untoward effects following iodized-oil injections in tuberculosis, that the lesson is not that which teaches against any particular substance being used, but rather against the procedure itself. The less the instrumentation, the less the introduction into the respiratory tract of any foreign substance in the presence of a recent or acute infection, be that infection tuberculous or nontuberculous, the fewer regrets we all shall have.

We have used iodized oil in tuberculosis patients or suspects for four main purposes:

1: For more clearly defining the extent and origin of fistulous tracts.
2: For more exact outlining tuberculous empyema cavities.

[1] From the Tuberculosis Pavilion, Ancker Hospital, St. Paul, Minnesota, and Pokegama Sanatorium, Pokegama, Minnesota.

3: For more accurate diagnosis of unexplained haemoptysis.
4: For further study of cases in which thoracoplasty has been unsuccessful.

As far as we have noted, tuberculous fistulae can be injected with iodized oil with impunity. Its superiority over bismuth is well known. It does not interfere with drainage, and does more definitely outline the tract. We have seen no untoward effects of any nature following its use.

In tuberculous empyemata, especially if they are localized, it is important to know the extent of the empyema cavity if surgery is to be considered. Iodized oil, injected into the empyema cavity, and films made with the patient in various positions will give a most accurate idea of its extent. The presence of a bronchial fistula is obviously of no moment as far as the use of the oil is concerned. Here again we have noted no undesirable results. With some we have aspirated the oil immediately after X-raying and in others we have permitted it to remain.

In using iodized oil intratracheally, in cases suspected of having tuberculosis because of unexplained haemorrhage, our thought, of course, has been bronchiectasis. Here we are not thinking of those advanced bronchiectatics with chronic cough, abundant sputum, etc. It is the dry bonchiectasis and the early one which we have in mind. We are convinced that no small number of cases that have been classified as "minimal tuberculosis" or "suspected tuberculosis" because of unexplained haemoptysis have a dry or early bronchiectasis. A certain number, and probably a fairly high percentage of such cases, will prove to be tuberculous after careful study and observation. Others, however, should be injected with iodized oil in the interests of more exact diagnosis, a thing most desirable in general, and especially so with tuberculosis a probability.

Two cases to illustrate:

1: Miss V. A.; age 40; clerk. Family history unimportant. *Past History:* Tuberculous cervical lymph nodes removed in 1902. Nervous breakdown in 1913. Had been veronal and alcohol addict. Pulmonary tuberculosis had never been diagnosed. Nothing in past pointing to chest.

Present Illness: August 10, 1926, while working began to spit up blood, about a half a cup. She was sent to the Ancker Hospital, and admitted to the tuberculosis pavilion. She stopped bleeding in a day or two, and after an additional ten days' rest was examined. Physical examination showed only the scars of the old operation on her neck. Her chest was quite clear, and X-ray films showed slight fibrosis in both apices but nothing which could be

interpreted as recent parenchymatous involvement. Her sputum was scant and negative repeatedly upon microscopic examination and guinea-pig inoculation. All other laboratory data were negative. After six uneventful weeks the patient bled again, but physical and X-ray examination showed no change. Two months later another two-ounce haemorrhage occurred, yet again without definite findings.

The patient refused iodized-oil injection, but submitted to bronchoscopy. This showed no cause for her bleeding, and through a misunderstanding no oil was injected by the bronchoscope. Following this the case progressed smoothly. The patient was being gradually put on exercise, when, in a temper, she left the hospital in May, 1927, under protest and with a diagnosis of pulmonary tuberculosis, minimal stage, improved. Following her discharge, she again raised blood.

In September, 1927, she committed suicide. At autopsy the trachea and lungs were removed *en masse* and injected with iodized oil. Films showed dilated bronchi in the left apex. Sections of the lungs confirmed this X-ray finding, and also showed definite scarring in both apices that was more marked on the left side but there were no tubercles anywhere. No other tracheal, bronchial or lung pathological changes were found.

We believed that the haemorrhage came, not from the congestive or erosive effects of caseating tubercle but from the apical bronchiectasis, which no doubt was the result of an anatomical tuberclosis of years' standing but of one which had never expressed itself clinically.

2: Mrs. J. E. M.; age 62; housewife. Family and marital history unimportant. *Past History:* Every spring for the past six or seven years had grippe, which left her with a cough but with scanty sputum for at least two months. Thought she had slight fever with cough.

Present Illness: On September 1, 1927, the patient suddenly began to have haemorrhages, and for three days raised about half a cup of blood each day, although she had not been coughing during the summer. She consulted a physician, who examined and X-rayed her, and told her she had tuberculosis.

One of us (E. K. G.) saw her on Semptember 22, 1927. She was coughing a little and her sputum was scanty and mucopurulent, but never malodorous. She was tired, had a poor appetite, and was quite worried over her condition. She had lost 10 pounds, and her temperature was 99.3° and pulse 100 at 3 P.M.

Physical examination showed scattered fine râles over the right lung anteriorly and a few posteriorly on the left. X-ray films showed a generalized increase of the linear markings in both lungs but no definite parenchymatous lesion. The sputum was negative for tubercle bacilli, and other laboratory data were also negative.

After iodized-oil injection chest films showed a small but definite bronchiectasis in the right lower lobe.

In patients with frankly demonstrable pulmonary tuberculosis we have, in the main, confined the intratracheal use of iodized oil to the study of thoracoplasty cases that have not exhibited the hoped-for benefit from the operation. The exceptions to this practice have been few. In one patient with left upper-lobe cavitation and also marked sinusitis both sides were injected before collapse, as bilateral bronchiectasis was suspected. In another, whose left upper-lobe lesion had cleared markedly but whose cough and sputum persisted, oil was injected because a residual bronchiectasis was suspected. This was found, along with a peculiar kinking of the left primary bronchus that was caused by upward retraction of the left root. And in two instances oil was used successfully to differentiate between cavitation and pleural annular shadows. We have refrained from routinely injecting all thoracoplasty patients before operation because we have been reasonably confident of the pathological conditions to be dealt with, as well as because of the general disfavor which iodized oil has acquired relative to tuberculosis. We have likewise kept from using the oil in general unless it promised to give useful information. In other words, we have not injected iodized oil intratracheally in tuberculosis patients just to see what would happen. But in postoperative thoracoplasty cases one will not infrequently have effected an apparently satisfactory collapse from an X-ray standpoint and still witness an annoying persistence of cough and sputum. Physical examination in many of these "problem cases" is not helpful, and the usual X-ray films may not be of assistance. Here iodized oil will often clearly explain the cause of failure by revealing unsuspected bronchiectasis or unclosed cavities, or both.

Perhaps if more thoracoplasty cases were injected before operation more preliminary phrenectomies would be done, especially in those cases exhibiting basal bronchiectasis. Archibald has alluded to this point. We think also that, in those cases with coexisting bronchiectasis, it would lead to a more extensive rib-resection, and thus to achieving a more complete collapse from the primary operation, thereby eliminating to a certain degree secondary interference, which in our experience has not been any too successful.

We have been most careful in selecting tuberculosis cases for the intratracheal injection of oil. All have been the "good chronic" that are so suitable for thoracoplasty, which implies a satisfactory general condition, and freedom from toxaemia, with no recent extension or exacerbation. Twenty cases in all have been injected and, with one possible

exception, no accidents, flare-ups, iodism or gastrointestinal disturbance have occurred. As a rule cough has been aggravated for a day or so, and mild transient febrile disturbances have been common.

The possible exception just referred to may well be given in more detail:

The patient was a man, age 32, who was admitted to Pokegama Sanatorium on January 8, 1926, with an advanced left-lung lesion. Under the usual regimen he gradually improved and after three months had a stable temperature and pulse. His cough and sputum improved somewhat. Eight months after admission films of his chest showed an annular shadow in his left lower lobe. His general condition was so good that iodized oil was injected to determine, if possible, whether he had a cavity or not. The oil was injected supraglottically without difficulty. The same evening the patient's temperature was 100.4° and this was accompanied by increased cough. His temperature went to 101.5° the next day, to 102° and 103.8° on the two subsequent days, and in three days more was running as it had before the injection. He seemed no worse for the experience; and films showed no new disease and no oil remaining in the cavity. Things went along smoothly for four more weeks, when suddenly the patient had a profuse haemorrhage and died. Whether this was the result of the oil, we, of course, cannot say. The interval of four weeks speaks against it. The character of the haemorrhage strongly suggests the rupture of a blood-vessel in a cavity, which iodized oil could hardly have caused. We also know from our films that the oil remained in the cavity for not quite three days. Unfortunately we could not obtain an autopsy.

The supraglottic method of introducing the oil has been used exclusively. Puncture of the cricothyroid membrane has seemed inadvisable because it would involve trauma to a mucous membrane, which in most of our cases was being bathed frequently with bacillary sputum. We have likewise avoided the bronchoscopic method, feeling that the instrumentation alone was not without danger for consumptive patients. And the deglutition method has not been used because it seemed to be taking unnecessary chances with the integrity of the gastrointestinal tract.

CONCLUSIONS

1. Iodized oil can be used with safety in tuberculous fistulae.
2. It causes no undesirable results in tuberculous empyema cavities.
3. It should be used for more exact diagnosis in unexplained haemoptysis.

4. It explains frequently the cause of failure in unsuccessful thoracoplasty cases.

5. It might be well to use it routinely preoperatively in thoracoplasty cases, in order to guide the surgeon regarding preliminary phrenectomy and as to the extensiveness of contemplated rib-resections.

6. The intratracheal use of iodized oil in tuberculosis patients is a relatively safe procedure if done by the supraglottic method in cases with chronic lesions.

PERIODIC FEBRILE EXACERBATIONS IN PULMONARY TUBERCULOSIS[1]

I. RAPPAPORT AND R. T. ELLISON

The two cases which we wish to discuss show a type of reaction in the course of pulmonary tuberculosis that has not received much attention in this country. We have become interested in this clinical type after reading the report of Burnand and Bothezat (1) on three cases and Glogauer (2) on two cases presenting this course.

The clinical history displayed by our two cases is one of periodic febrile exacerbations with entirely apyretic intervals, occurring in the course of chronic pulmonary tuberculosis. These periods of fever occur at irregular intervals and generally last for from four days to a week. All the cases (the five referred to above and the two presented herewith) have certain characteristics in common. All were males except one of ours, all were chronic cases of fibrocaseous or fibroulcerative type, and all showed cavitation. In the cases that came to autopsy the cavities were found to be large, with thick fibrous walls, and to be surrounded by the atelectatic and cirrhotic remains of pulmonary tissue. The X-ray films of our two cases confirm this. At the time of the febrile exacerbation there is generally very little general disturbance. Glogauer describes an "aura" of malaise and anorexia, but we have found little change in the subjective symptoms. The daily amount of sputum does not vary much during the exacerbation from the patient's normal amount but both of our cases had signs of congestion in their chests during the up-grade of the exacerbation, with a feeling of incomplete "cleaning out" of the chest. During the decline of the fever they felt that the "cleaning out" was more complete and easier. The sputum at this time was always thin, of purulent appearance, and had "a bad taste." There was always an increase in appetite and frequently a feeling of well-being after one of these attacks.

The three cases of Burnand and Bothezat are given as chronic fibro-

[1] From the Home for Consumptives, Chestnut Hill, Philadelphia, Pennsylvania.

caseous and fibroulcerative in advanced stages. One is described as having a large cavity, but the other two both had cavities in their lungs; in fact a large cavity was found in one when it came to autopsy. Their exacerbations lasted three to four days at intervals of from sixteen to forty-four days. The patients had transient congestive manifestations during their exacerbations, but otherwise cough, expectoration and general constitutional symptoms remained largely unaltered. Analyzing the possibilities as to the cause of these attacks Burnard and Bothezat came to the following conclusions:

1: Active evolution of the tuberculous process can be ruled out by lack of evidence of pulmonary extension over long periods of observation.
2: Intracavity retention is not probable in view of the lack of blockage symptoms before and during the attack.
3: Miliary dissemination of a partially localized type cannot be ruled out, but there is no evidence to support it.
4: Biological changes in the tubercle bacillus is a far-fetched hypothesis.
5: Neurovegetative periodicity may be ruled out by the absence of other endocrine symptoms.
6: Alternating immunological phenomena in the patient can be thought of as a very plausible hypothesis, and one that is not without some phenomena to support it.

Glogauer describes his cases as distinctly of the chronic extensive cavity and advanced cirrhotic type. His first case, which came to autopsy, showed a cirrhotic and atelectatic shrinkage of the entire lung with a huge central cavity. His second case showed a similar excavation in one lung surrounded by a thick cirrhotic wall. The exacerbations in these cases did not occur at such regular intervals, and their duration was not as limited as in the cases previously referred to. Glogauer agrees with the first authors in ruling out all the above-mentioned possible causes of the attacks and even rejects that favored by Burnand and Bothezat, supporting his opposition on their own reports of the cases treated with tuberculin, which did not show any variation in reaction during the exacerbation. Glogauer calls attention to the fact that the existence of large cavities is the most conspicuous feature common to both of his cases, thus suggesting some connection between this and the peculiarity of the clinical course. Glogauer leaves the question open to further investigation.

In presenting our two cases we believe the attached X-ray and tem-

perature charts speak for themselves and all we need to add are the following clinical notes:

Case 1: A man, 48 years old, who had chronic pulmonary tuberculosis for the past six years. He ran a similar clinical course for two years previous to the beginning of the temperature record as presented here, but he has had no further rises in temperature since the last one recorded here. This man has made a remarkable recovery, and six months ago was discharged to return to his former work as an engraver. He has remained well since then and has continued to work. Anatomically the right upper lobe was converted into a huge cavity surrounded by an unusually thick wall of massive cirrhosis. Although this wall appeared to be thick and unyielding at first, it eventually was compressed by the surrounding emphysema, and finally was greatly reduced in size as can be seen by comparing the two films.[2]

Case 2: A woman, 34 years old, who has had pulmonary tuberculosis for the past six years. For some time following the period covered by the attached chart she continued to have only periodic febrile reactions, but later she began

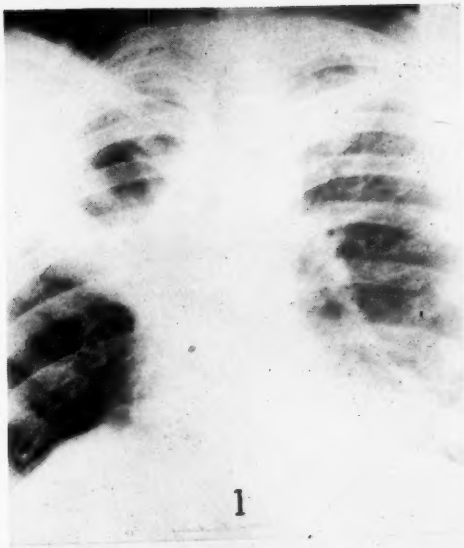
FIG. 1. CASE 1, DECEMBER 9, 1924
FIG. 2. CASE 1, APRIL 21, 1927
FIG. 3. CASE 2, DECEMBER 12, 1926

to lose ground, a septic temperature developed, and now she has almost reached the end of the journey. Anatomically she presented a dense cirrhotic and atelectatic shrinkage of the entire left lung, which contained a large cavity. Her liver extends downward to the level of the umbilicus, and the spleen protrudes three fingers breadth beyond the costal margin. She also has a dense cloud of albumen in the urine.

DISCUSSION

The above two cases show the typical clinical course described by the continental authors. Although no X-ray pictures of the other cases could be compared with ours, fortunately autopsy records published in these contributions give the description of the anatomical lesions of their cases, and show that large excavations are the common feature in all. In the study of our cases the connection between the unusually massive cirrhotic cavities and the peculiar clinical course has been so impressive that it seemed quite natural to us that Glogauer should have likewise

[2] In spite of this obvious improvement the ultimate outcome is doubtful as amyloid disease with a high albumen content in the urine is present.



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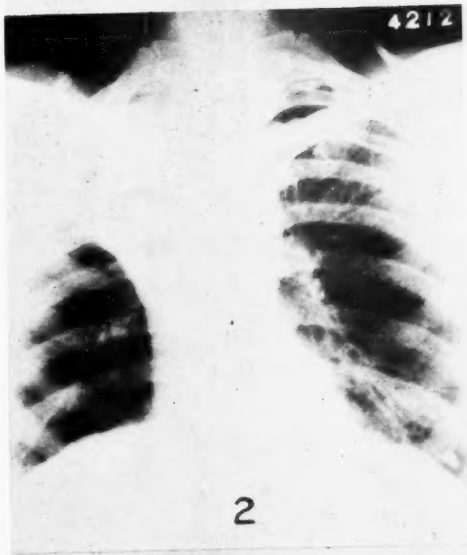

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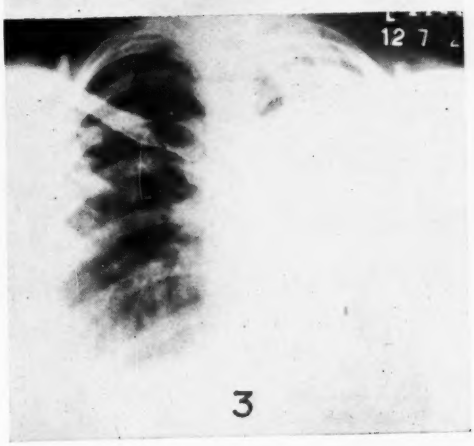

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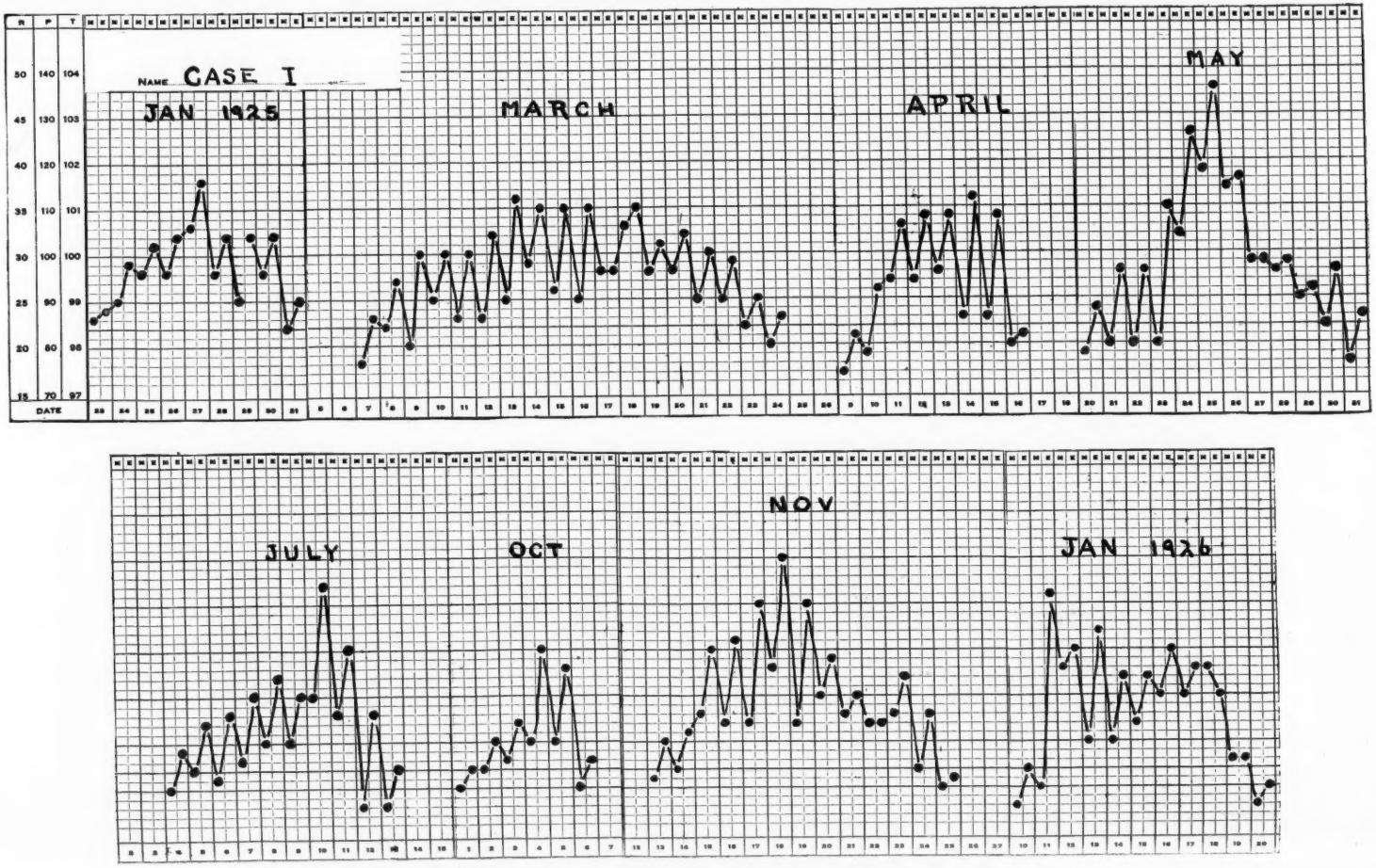

Chart 1. Temperature Chart of Case 1

Chart 1. Temperature Chart of Case 1

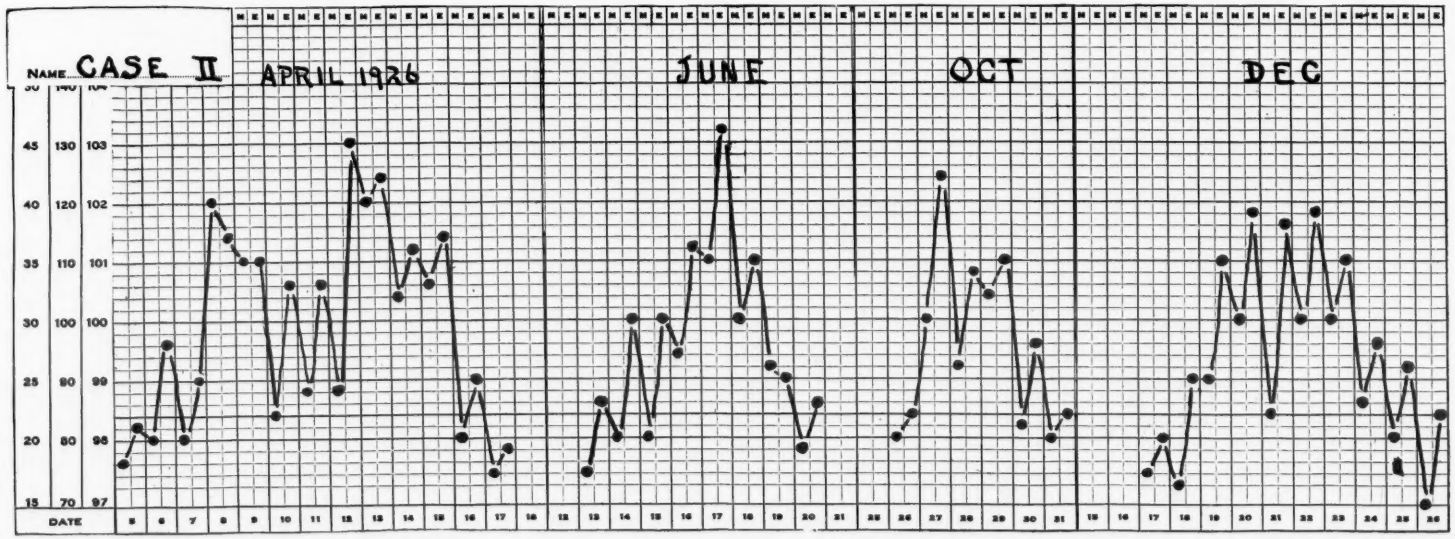

Chart 2. Temperature Chart of Case 2

been impressed. We believe that, at least as far as our cases are concerned, this connection is beyond doubt valid. Our conception is that a purulent process taking place upon the surface of the wall of the cavity is the most acceptable explanation of the periodic attacks of fever. The determination of the exact nature of the lesion and the character of the infection are of course beyond the reach of bedside observation. Glogauer mentions a publication of Zuccola, to which we have not had access, in which two cases of periodic exacerbations are reported, and which described cutaneous efflorescences and that *Staphylococcus aureus* was recovered from their contents. The evidences that speak for the septic nature of the exacerbations are the following:

1: While they are very unlike any corresponding manifestations seen in the great variety of tuberculous processes they are almost identical with septic processes of similar extent.
2: They lead to amyloid disease and secondary anaemia, even though their course is temporarily favorable.
3: They leave concurrent tuberculous processes not only uninfluenced, but are actually not incompatible with the healing and absorption of such processes.
4: They are accompanied by the temporary discharge of a noisome purulent material in the expectoration of the patients.

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CASES OF ERYTHEMA NODOSUM WITH NEGATIVE TUBERCULIN TESTS[1]

ELSA LAGERGREN

The relation between erythema nodosum and tuberculosis has long been discussed. Nearly all the cases of erythema nodosum at the Göteborg (Sweden) Children's Hospital during the years 1922–1927 have shown a close connection with tuberculosis both as to the possibility of contagion before the appearance of the nodules and as to the development of typical tuberculous symptoms during or after the erythema; for instance, besides the positive tuberculin reaction, there has been involvement of the hilum and bronchial lymph nodes (1), pleurisy with effusion, etc. (2). For this reason it has been of special interest to follow up more closely the few cases in which it has been impossible to discover such a relation, and in which some other aetiology must therefore be sought.

The great infrequency of these cases, 6 in six years, is in itself remarkable when compared with the number of patients with erythema nodosum treated in the hospital during this period, namely 142, to which must also be added about 40 ambulatory cases. Only in these 6 cases have repeated tuberculin tests given a negative reaction during the illness until at least one month after it. In 3 of the 6 cases we have also been able to make tuberculin tests 1 year, 7 months and 5 months, respectively, before the patient was taken ill; these tests also gave negative results. In this latter respect these cases do not differ from those in which tuberculous infection can be proved during or after the eruption. In making the tuberculin tests we have always employed, first, the Pirquet epidermal test, followed up by the Mantoux intracutaneous test, using increasing dosages of Old Tuberculin; usually the dose has not exceeded 3 mgm., but in 3 cases 10 mgm. was used.

Case Reports

1: A 7-year-old girl, S. G. Her mother had died of heart disease in 1924, but she had suffered from consumption for several years. A brother had been treated at this hospital for tuberculosis of the bones. Our patient had been declining during the summer of 1925 and on admission to the hospital in September, 1925, had widespread, typical lesions of erythema nodosum.

[1] From the Children's Hospital, Göteborg, Sweden. (Superintendent, Dr. Arvid Wallgren.)

During her stay at the hospital 10 Mantoux tests were made. A Pirquet test, September 17, 1925, was negative. The results of the Mantoux tests are given in table 1.

TABLE 1

Results of Mantoux tests

DATE	DOSAGE OF TUBERCULIN	RESULT
1925	*mgm.*	
September 18	0.001	Negative
19	0.01	Negative
21	0.1	Negative
22	1.0	Negative
23	3.0	Negative
24	10.0	Negative
October 2	3.0	Negative
3	10.0	Negative
5	10.0	Negative
16	3.0	Negative

Roentgen-ray examination of the lungs did not reveal any pathological condition. The patient was discharged in good health shortly after the last Mantoux test was made. In the spring of 1926 she became an ambulatory patient in the surgical outpatient department and was treated for scrofuloderma-like lesions on her forearms. Unfortunately, no definite report on the nature of the eruptions was made. A tuberculin test was not made. In December, 1926, I examined her and obtained a positive Pirquet reaction and a strongly positive Mantoux reaction with 0.1 mgm. of tuberculin. Roentgenographs of the lungs were still negative, and the patient was well and strong.

2: E. N., a 14-year-old boy. His mother's cousin, who died in 1922 or 1923 of tuberculosis, had met the patient several times. He had not been exposed to tuberculosis otherwise as far as his mother knew. He became ill with fever on April 13, 1926. On the 17th he was admitted to the hospital with typical erythema nodosum. During his month's stay at the hospital Pirquet tests, made on April 20 and 21, were negative. Mantoux tests are given in table 2.

TABLE 2

Results of Mantoux tests

DATE	DOSAGE OF TUBERCULIN	RESULT
1926	*mgm.*	
April 22	0.01	Negative
23	0.1	Negative
24	1.0	Negative
25	3.0	Negative
27	3.0	Negative
30	10.0	Negative
May 18	3.0	Negative
21	10.0	Negative

Roentgenographs of the lungs were negative.

In August the patient returned for further tuberculin tests. On August 23 the Pirquet test was negative; on August 25 the Mantoux test with 0.1 mgm. of tuberculin was negative; on August 27 this test with 1.0 mgm. was negative and on August 30, with 3 mgm., it was negative. In November of the same year another Pirquet test resulted in a weakly positive reaction. A Mantoux test with 1.0 mgm. of tuberculin the same day caused a very strong reaction. Roentgenographs of the lungs did not reveal any evidence of a pathological condition.

3: A 12-year-old girl, A. B., whose mother living in the home had suffered from tuberculosis for several years, at the first examination made at the Göteborg Children's Hospital in February, 1924, gave a negative reaction to the Pirquet and the Mantoux tests with 2.0 mgm. of tuberculin. Roentgen-ray examination revealed an enlargement of a paratracheal lymph node. Otherwise the patient was in perfect health. She returned to the hospital in July the same year with a widespread erythema-nodosum eruption, which had appeared on July 27.

TABLE 3

Results of tuberculin tests

DATE	DOSAGE OF TUBERCULIN	RESULT
1924		
August 1	Pirquet	Negative
5	Pirquet	Negative
7	Mantoux 1 mgm.	Negative
8	Mantoux 3 mgm.	Negative
10	Mantoux 10 mgm.	Negative
16	Mantoux 3 mgm.	Negative

The roentgen observations were not typical of tuberculosis. After about two weeks, the patient was discharged in good health. At a subsequent examination in April, 1927, the Pirquet test was negative. The Mantoux tests with 1 and 3 mgm. were also negative, but with 6 mgm. the test was positive (weak reaction, probably nonspecific).

4: A 13-year-old boy, N. M., who had two consumptive sisters and one brother, who had had erythema nodosum in 1923, had had erythema nodosum in 1921 shortly after he had had diphtheria. The condition had been diagnosed by a physician, but neither a tuberculin test nor a roentgen examination had been made. In March, 1923, he came to the outpatient department. He had then had fever for about six weeks. On March 21 the Pirquet test was negative. Nothing abnormal was found in the lungs except a slight enlargement of the hilum lymph nodes. The fever disappeared after three weeks. On May 5

the Pirquet test was negative and the results of the roentgen examination were the same as before. In September of the same year roentgen examination showed improvement, and the Pirquet test was again negative.

In May of the following year the patient again visited us. He had then profuse erythema-nodosum lesions on both arms and legs, and a subfebrile temperature. The roentgen picture was unchanged.

On May 5, 1924, the Pirquet test was negative; on May 19 it was also negative (the nodules were still numerous). On May 21 the Mantoux test with 1 mgm. of tuberculin was negative; on May 23 with 3 mgm. it was negative. The fever disappeared on May 25. In August the Mantoux test with 3 mgm. was strongly positive. The patient had been well and strong during the entire past year. In the fall of 1926 I made new tuberculin tests and obtained a negative reaction with the Pirquet, while a Mantoux test with 3 mgm. on the same day gave a strongly positive reaction. The boy had continually been in good health. Roentgen examination did not show any pathological condition.

5: A 5-year-old girl, B. A., at the age of 2 years, according to the mother's statement, had had an attack of a skin disease, which had been diagnosed as erythema nodosum. An uncle, who suffered from consumption, often visited her home. The patient had never been strong and had often had periods of fever. When examined at the hospital in May, 1924, she gave a negative Pirquet reaction and the roentgen examination did not show any pathological condition. In December, 1924, she was admitted to the hospital with typical erythema-nodosum lesions.

Roentgen-ray did not reveal any pathological condition. The results of tuberculin tests are given in table 4. The patient was discharged after one week, and soon recovered fully. When examined in November, 1926, and in April, 1927. she was perfectly well and gave negative reactions to tuberculin tests as shown in the table.

TABLE 4

Results of tuberculin tests

DATE	DOSAGE OF TUBERCULIN	RESULT
1924		
December 15	Pirquet	Negative
16	Mantoux 0.1 mgm.	Negative
18	Mantoux 1.0 mgm.	Negative
20	Mantoux 3.0 mgm.	Negative
1926		
November 16	Pirquet	Negative
18	Mantoux 1.0 mgm.	Negative
20	Mantoux 3.0 mgm.	Negative
1927		
April 12	Pirquet	Negative
12	Mantoux 1.0 mgm.	Negative
14	Mantoux 3.0 mgm.	Negative

6: A 9-year-old girl, I. W., whom we had not had the opportunity to examine before she became ill with erythema nodosum, had never been sick before, and her mother did not know of any source of tuberculous infection. It may be of interest to note that we have later had under our care at the hospital two other patients with erythema nodosum, who lived in the same house as I. W., and who both had tuberculous relatives living in their homes. It is probable that I. W. also had been in more or less intimate contact with these relatives.

I. W. was examined here for the first time in October, 1924. She had then had an erythema for two weeks and was without fever. There were typical lesions on both legs below the knees. Roentgen examination did not reveal any specific evidence of tuberculosis. On October 19, 1924, the Pirquet test was negative. On October 13 the Mantoux test with 1.0 mgm. of tuberculin was negative. On November 11, the Pirquet test was again negative.

The patient was not admitted to the hospital, but was examined in the outpatient department. A month later a new Pirquet test was negative. She had been well and strong during this time. Tuberculin tests, made in December, 1926, and April, 1927, were negative.

TABLE 5

Results of tuberculin tests

DATE	DOSAGE OF TUBERCULIN	RESULT
1926		
December 20	Pirquet	Negative
22	Mantoux 1.0 mgm.	Negative
1927		
January 1	Mantoux 3.0 mgm.	Negative
April 12	Pirquet	Negative
12	Mantoux 1.0 mgm.	Negative
14	Mantoux 3.0 mgm.	Negative
16	Mantoux 6.0 mgm.	Negative

A roentgen examination did not reveal any abnormality.

During the 2½ years since she had had erythema nodosum the patient had been doing well with the exception of a few attacks of tonsillitis. She had never had any pains in the joints.

COMMENT

Thus in 6 cases of erythema nodosum, 4 in girls from 5 to 12 years of age, and 2 in boys, 13 and 14 years old, at least 5 had been in contact with some source of tuberculous infection in the home, and the sixth had such a source of infection in the house that she was living in. In all the

cases there were typical lesions of erythema nodosum accompanied by more or less fever which soon disappeared. The general condition was good, and there were no symptoms from the joints or any other signs of disease, except in two of the cases, in which there was a slight enlargement of the hilum and bronchial lymph nodes, which was discovered by roentgen examination. In both of these cases, however, the pathological processes were not revealed at the time when the erythema appeared, but were discovered at earlier examinations made 1 year and 5 months, respectively, before the appearance of the erythema. One of these two patients had also had an attack of proved erythema nodosum three years before. Another of the 6 patients had also had an earlier attack.

In my subsequent examinations, 4 of these 6 patients showed positive tuberculin reactions, 7 months, 1, $1\frac{1}{4}$, and $2\frac{3}{4}$ years after the erythema. In the last-mentioned case, the reaction was only weakly positive to a Mantoux test with 6 mgm. of tuberculin; perhaps therefore this case should not be included among the positive cases. During the intervening period none of the patients had been sick, and roentgen examinations, made at the same time as the positive tuberculin reactions were obtained, did not show any pathological condition. So far as is known the patients had not been more intimately exposed to tuberculous infection than they had been before.

In the remaining two cases the reactions were still negative when tests were made about $2\frac{1}{2}$ years after the erythema had disappeared. Both the children enjoyed good health all the time.

As regards the aetiology of erythema nodosum, three different causes have usually been especially considered: namely, tuberculosis, rheumatic infection, and other specific infection. In the 6 cases reported here, tuberculosis can fairly certainly be excluded during the erythema, as the tuberculin reactions have been negative and no definite symptoms of tuberculosis have been present; this statement is made on the presumption that the prevailing opinion of the significance of a negative tuberculin test, performed *lege artis*, is correct. The exposure to tuberculosis to which 5 of the children can be proved to have been subjected is, however, remarkable. That the tuberculin reaction in 2 or 3 of the cases has become positive a long time after the erythema nodosum had disappeared can perhaps be explained by the fact that these patients at the time of the onset of their illness, and for some time afterward, for some unknown reason were anergic (3), and later also for an unknown reason became allergic. This is, however, absolutely contradictory to the observations

generally made in other cases of erythema nodosum in our hospital, that the lesions appear just at the time when there is a change from the anergic into the allergic condition (4), and that patients with erythema nodosum show an unusual sensitiveness to tuberculin.

There are also no indications that a rheumatic infection is an aetiological factor in these cases, as in none of them were there pain in the joints, any objective pathological process of the joints, heart disease, chorea, or any other symptoms characteristic of rheumatic fever.

Thus the question remains whether erythema nodosum cannot sometimes be a disease *sui generis*. Most of the cases reported as such in the literature have shown positive tuberculin reactions and have generally been followed by a proved tuberculous condition, and therefore the relationship to tuberculosis can hardly be absolutely disregarded. In the 6 cases described in this article, on the other hand, it seems quite possible that an unknown specific infection was the cause of the erythema nodosum, or that some nonspecific allergic reaction of the body had taken place.

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THE SICKLE-CELL PHENOMENON IN TUBERCULOSIS PATIENTS[1]

VERA B. DOLGOPOL AND RICHARD H. STITT

The term *sickle-cell phenomenon* is used to designate peculiar morphological changes of the erythrocytes which apparently are observed only in the negro race. It comprises the cases of true sickle-cell anaemia and the cases of "latent sickling" (Sydenstricker, Mulherin and Houseal (1)) or of "sickle-cell trait" (Hahn (2)). Among other terms used for these two conditions the best and most adaptable for universal use are the terms *meniscocytic anaemia*, introduced by Miyamoto and Korb (3), and *meniscocytosis*, proposed by Graham and McCarty (4).

The *meniscocytic anaemia*, or the *sickle-cell anaemia*, is a disease manifesting itself in an infantile general development and in an anaemia, with a marked haemolysis and with an increased haematopoiesis. On fixed and stained blood-smears a number of crescent-shaped erythrocytes are seen; the number of these cells increases greatly in moist-chamber preparations a few hours after mounting. Other frequent manifestations of this disease are abdominal and rheumatoid pains and leg ulcers.

The *meniscocytosis*, or the *sickle-cell trait*, is encountered in perfectly healthy and normally developed individuals. In meniscocytosis neither haemolysis nor increased haematopoiesis is observed. Fixed blood-smears do not contain any crescent-shaped erythrocytes; in moist-chamber preparations, however, a certain number of erythrocytes assume crescentic, stellate and other bizarre forms, with numerous thread-like excrescences. Cases of meniscocytosis can usually be found among healthy members of the families of patients with meniscocytic anaemia.

The incidence of the sickle-cell phenomenon has been discussed in several articles devoted to this subject. Cooley and Lee (5) report the incidence as being 7.5 per cent (30 in 400 cases examined). Graham and McCarty in their two series of investigations found incidences of 5.2 per cent (14 in 250 cases) and of 7.2 per cent (44 in 608 cases examined). Miyamoto and Korb found 19 cases in 300 cases examined (6.3 per cent). Sydenstricker, Mulherin and Houseal reported in their earlier investiga-

[1] From the Pathologic Laboratories, Sea View Hospital, Staten Island, New York.

tion 13 cases in 300 negroes examined (4.3 per cent). Later Sydenstricker (6) reported the incidence as being 0.25 per cent, and Mulherin and Houseal (7) mentioned the rate of 0.6 per cent. The frequency of the true sickle-cell anaemia, as compared to the sickle-cell trait, is 1:9, according to Sydenstricker (8).

An investigation of the incidence of the sickle-cell phenomenon, carried out on tuberculous negro patients of the Sea View Hospital, gave the rate of 5.2 per cent. In 77 cases examined there were 4 cases of sickle-cell phenomenon (3 cases of meniscocytosis and one case of meniscocytic anaemia; the mother of the boy with meniscocytic anaemia showed the evidence of meniscocytosis, but we did not include this case in the calculation, following the example of other investigators, who usually excluded the members of the families in their estimation of incidence of the phenomenon).

Combining the actual figures of cases examined and of cases of sickle-cell phenomenon found by all the above-named investigators, the rate of 6.5 per cent is obtained (110 cases of sickle-cell phenomenon in 1,685 cases examined). Judging from the rate obtained from this number of cases, the figures given by Sydenstricker (0.25 per cent) and by Mulherin and Houseal (0.6 per cent) in their last investigations are decidedly too low.

The investigation of the incidence of the sickle-cell phenomenon was carried out in the following way:

Two or three moist-chamber blood preparations were made from each negro patient. The blood was withdrawn from the finger, enclosed between an ordinary slide and a cover-slip, and sealed with paraffin. The preparations were kept at room temperature and were examined three times: half an hour, twenty-four hours and forty-eight hours after mounting. In the cases in which the sickle-cell phenomenon was noticed, further blood study was made. The additional blood examinations included the following: additional moist-chamber preparations, erythrocyte count, leucocyte count (including the differential count), haemoglobin, color index, vital staining, fragility test, Wassermann, and, in cases with greenish or bright yellow blood-serum, qualitative van den Bergh test. A blood culture was taken on the patient with meniscocytic anaemia. The urine was examined for urobilin and urobilinogen. The stool was examined for parasites and ova.

In moist-chamber preparations the sickle-cell phenomenon became evident within 24 hours, except in the case of meniscocytic anaemia, in

which it was evident immediately. The phenomenon not having appeared within 24 hours did not manifest itself later. In the cases of meniscocytosis *all* moist-chamber preparations (10 to 12) contained the characteristic bizarre cells with numerous excrescences. The number of these cells varied considerably in different preparations from the same blood, being sometimes limited to a few cells on one preparation, while other preparations contained a far greater number of bizarre cells. The majority of characteristic cells were located in the central portion of the drop, while at the periphery they were less numerous (a similar observation was previously made by Graham (9)). The cause of this distribution may be explained on the basis of experiments of Hahn and Gillespie (10). These authors established the following facts: (1) that contact with oxygen prevents the formation of crescent-shaped cells in the cases of sickle-cell trait; (2) that oxygen restores the circular configuration of the crescent-shaped cells; (3) that in chambers filled with ethylene the majority of crescent-shaped cells are situated at the periphery of the drop. These findings may be formulated in the following way: asphyxiation stimulates the formation of crescent-shaped erythrocytes. In ordinary moist-chamber preparations the greatest degree of asphyxiation can be expected in the central portion of the drop, while the periphery of the drop remains in contact with the oxygen of the air included in the chamber. A greater prevalence of crescent-shaped and bizarre cells in the central portion of the drop can therefore be explained by deficiency of oxygen in this part of the drop.

In the case of meniscocytic anaemia the fragility of the erythrocytes was considerably diminished (beginning haemolysis at 0.36 per cent NaCl, complete haemolysis at 0.12 per cent). In two cases of meniscocytosis the respective figures were 0.44–0.24 and 0.38–0.18. Van den Bergh's indirect reaction was positive only in the case of meniscocytic anaemia. Urobilinuria was present in the case of meniscocytic anaemia and in one case of meniscocytosis (case 2). Eosinophilia and intestinal parasites (ova of ascaris lumbricoides and of trichiuris trichiura) were found only in the case of meniscocytic anaemia.

Case Reports

Case 1: G. R., colored male, 13 years of age. Admitted on July 12, 1927. Born and always lived in Cuba with his grandmother until nine months ago. The parents and other children of the family lived in New York for the past ten years. The boy and his mother have no knowledge of any diseases in the past. The patient began to cough five weeks before admission, was taken to a

dispensary and from there directed to the Sea View Hospital. *Physical Examination:* A colored boy, undernourished, with a physical development of child of 9. Weight 46 pounds. Sclerae yellowish-green in color. *Lungs:* (X-ray report): Moderately advanced bilateral acinous tuberculosis. *Heart:* Apex-beat on nipple line or, sometimes, 1 cm. to the left. Systolic murmur, inconstant and nontransmissible, over the apex. *Bruit de diable* over the veins of the neck. Liver slightly enlarged. Spleen not palpable. No ulcers or scars on the legs. The blood examination revealed a meniscocytic anaemia. The number of crescent-shaped cells was 30 per cent in stained blood-smears. In moist-chamber preparations the number of these cells increased to 80 per cent. Haemoglobin 40–45 per cent. Erythrocytes 2,260,000–2,590,000, color index 0.9. Leucocytes 10,000–13,000. Polynuclears 50–37 per cent. Eosinophiles 7–4 per cent. Normoblasts 7 to 100 leucocytes. Vital staining gave 3 per cent of reticulated cells. Blood-culture negative. Fragility of the erythrocytes 0.36–0.12 per cent NaCl. Van den Bergh indirect reaction positive (direct, greatly delayed, slightly positive). Wassermann 4 plus; after antisyphilitic treatment (neoarsphenamin and bismudol) the Wassermann reaction became negative, but the character of the cells did not change, although the percentage of haemoglobin and the number of erythrocytes increased. The urine was positive for urobilin and urobilinogen, negative for bile pigments. Stool contained ova of ascaris lumbricoides and of trichiuris trichiura, but no parasites. No ova of *necator americanus* found on repeated examinations. The patient gained 10 pounds in one year. The patient's mother, a healthy woman weighing about 180 pounds, showed meniscocytosis in moist-chamber blood preparations. Her blood Wassermann was negative.

Case 2: W. E. B., a colored male, 23 years old, admitted on June 9, 1928. *Past History:* Measles, whooping-cough; gonorrheal infection four years ago. *Present illness* began 4 months ago with night-sweats, loss of weight, cough. Nine weeks before admission to Sea View Hospital underwent rib-resection in another hospital. *Physical Examination:* Adult male, poorly nourished, dyspnoeic, toxic. The nails are cyanotic. No ulcers or scars on legs. No discoloration of the sclerae. *Lungs:* Far-advanced pulmonary tuberculosis; empyema of the right pleural cavity, reaching the fourth rib anteriorly, with discharging operative sinuses. *Heart:* Displaced to the left; first sound indistinct; no murmurs. Blood examinations on June 27 and July 27 showed the following: haemoglobin 45 per cent, erythrocytes 3,030,000, color index 0.75, leucocytes 6,800, polynuclears 77 per cent. No erythroblasts, no reticulated cells. Fragility of the erythrocytes 0.38–0.18 per cent NaCl. Blood-serum greenish in color; van den Bergh indirect reaction negative. Moist-chamber blood preparations show a large number of bizarre cells with numerous excrescences, 24 hours after mounting. Urobilinuria present. In August, 1928,

the pleural effusion reached the second interspace anteriorly. The patient died August 26, 1928.

The blood of three other dying patients, examined 3 to 10 days before death, did not show any morphological changes of the erythrocytes.

Case 3: M. G., a colored girl, 11 years old. Born and always lived in New York City. Admitted in April, 1928, with the complaint of loss of weight. *Previous Illnesses:* Whooping-cough and measles. *Physical Examination:* General development of a child of 11. The sclerae are white. *Lungs:* Incipient tuberculosis of the right apex. *Heart:* Normal borders, no murmurs. *Blood Examination:* Moist-chamber preparations show bizarre forms of the erythrocytes 24 hours after mounting, erythrocytes 5,000,000, haemoglobin 100 per cent, no erythroblasts, no reticulated cells. The blood-serum presents no discoloration. No urobilinuria.

Case 4: J. M., a colored male, 36 years old. Born in Florida; lived there to the age of 20. *Previous Illnesses:* "Yellow jaundice" at the age of 17; erysipelas shortly before admission. Admitted in June, 1927, with complaint of weakness following erysipelas. *Physical Examination:* Well-developed, well-nourished male. *Lungs:* Bilateral tuberculosis of the lymph nodes of the hilum. *Heart:* No murmurs; second aortic sound accentuated. Spleen not enlarged. No leg ulcers or scars. No discoloration of the sclerae. *Blood Examination:* Bizarre shapes of erythrocytes in moist-chamber preparations 24 hours after mounting, haemoglobin 100 per cent, erythrocytes 5,000,000, no erythroblasts, no reticulated cells. The blood serum presents no discoloration. No urobilinuria.

Case 1, the case of meniscocytic anaemia, supports the established opinion that syphilis is not an aetiological factor in the development of the meniscocytic anaemia. The patient's blood picture remained essentially unchanged after successful antisyphilitic treatment.

It is of interest to compare cases 1 and 2 in regard to the aetiology of the meniscocytic anaemia.

Hahn and Gillespie advanced a theory that prolonged anoxaemia in chronic lung and heart diseases may produce an active meniscocytic anaemia in individuals with hereditary meniscocytosis. In analyzing the cases of sickle-cell anaemia reported in the literature and observed in their practice, Hahn and Gillespie found that the majority of patients presented organic heart lesions, and were therefore inclined to explain the development of the meniscocytic anaemia as due to the influence of chronic anoxaemia.

The patient G. R. (case 1), with a typical picture of meniscocytic anaemia, did not show any evidence of anoxaemia. His tuberculous lung lesion was insufficient to impair the function of the lung. The heart lesion was apparently functional and anaemic (the systolic murmur was not constant, nor transmissible). Since his general condition improved, he participated in all permitted activities without suffering from dyspnoea.

On the other hand, the patient W. E. B. (case 2), with plain meniscocytosis and with a severe secondary anaemia, did not show any evidence of meniscocytic anaemia, regardless of an extensive tuberculous lesion of the lungs and of a large empyema causing dyspnoea and cyanosis. A somewhat increased resistance of the erythrocytes and the presence of urobilinuria, usually observed in meniscocytic anaemia, would not justify a diagnosis of meniscocytic anemia in this case, because these changes were seen in a number of tuberculous patients without meniscocytosis.

Anoxaemia, due to an extensive pulmonary tuberculosis and to compression of the lung by a pleural effusion, apparently is not the stimulus which would change the meniscocytosis into meniscocytic anaemia. A severe secondary anaemia superimposed on hereditary meniscocytosis does not change the shapes of erythrocytes in the characteristic crescents and does not increase the haematopoiesis.

Among aetiological factors in the development of meniscocytic anaemia Jaffé (11) mentions a cold, tuberculosis, syphilis, pneumonia, nephritis, malaria, frambesia, and amoebic dysentery. Judging from two cases discussed above, we think that at least two aetiological factors, tuberculosis and syphilis, must be taken off this list.

The frequent occurrence of organic heart lesions in meniscocytic anaemia, on which Hahn and Gillespie based their theory, and recurrent rheumatic pains often accompanied by fever (Hein, McCalla and Thorne) (12) suggest rather that at some period of their lives the patients' bloodstream must have been invaded by microörganisms which have a predilection for serous surfaces. The streptococcus is the microörganism which usually attacks the serous surfaces.

In meniscocytic anaemia the streptococcus has been isolated from the organs only in two instances. Graham (9) isolated a haemolytic streptococcus from the lungs of his patient who died of pneumonia; on this occasion he suggested that the streptococcus may be an aetiological factor in the development of the meniscocytic anaemia. Hahn and Gillespie isolated a green-producing streptococcus from the excised spleen of their

patient. The fact that blood-cultures made on several patients with meniscocytic anaemia were always found negative does not contradict the theory of bacterial influence on the blood or blood-forming organs, because it is possible that the blood was cultured at the time when the bacteriaemia had subsided and only its late after-effect, the meniscocytic anaemia, was evident.

SUMMARY

1. The incidence of the sickle-cell phenomenon in 77 tuberculous negro patients was found to be 5.2 per cent.

2. The incidence of the sickle-cell phenomenon in 1,685 cases examined by different investigators is 6.5 per cent.

3. In the hereditary meniscocytosis a greater prevalence of bizarre cells in the central portion of moist-chamber blood preparations is due to a greater asphyxiation of the erythrocytes in the centre of the drop.

4. Chronic anoxaemia, caused by a disease or compression of the lungs, is not an aetiological factor in the development of the meniscocytic anaemia from hereditary meniscocytosis.

5. Tuberculosis, syphilis and secondary anaemia cannot be regarded as aetiological factors in the development of the meniscocytic anaemia.

We wish to thank Dr. Francis X. Murray, Dr. Ernest Newman and Dr. Alexander Strelinger for permission to work on their patients in connection with this investigation.

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THE TREND OF TUBERCULOSIS MORTALITY IN RURAL AND URBAN AREAS[1]

EDGAR SYDENSTRICKER

An increasing interest in the epidemiology of tuberculosis, belated as it is after thirty years of organized efforts to control the disease, is stimulating a closer scrutiny of the mortality and other data relating to factors involved in its behavior as a social and biological phenomenon. Those who are scientific in their interest in the subject naturally are concerned first with the accuracy and detail of the statistics of the disease. Having evaluated the statistics, their next concern is with records of the status of, and changes in, factors that influence its incidence and its course.

The study of tuberculosis death-rates in rural and urban areas is a case where the epidemiologist is concerned with the course of the disease, so far as mortality rates can depict it, under conditions that are dissimilar in certain respects. Some two years ago Krause (1) referred to the indications afforded by urban and rural tuberculosis mortality statistics *as recorded*, that in New York State the tuberculosis death-rate in rural districts apparently was not only declining more slowly than that in urban districts but it had actually exceeded the urban rate since 1920. Precisely the same indications, it may be noted, are given by officially recorded urban and rural tuberculosis mortality rates for the group of other States (2) comprising the "original" registration area[2] and plotted in figure 1. Now, if this statistical indication were true, we would have an important fact upon which, taken into consideration with other data, interesting hypotheses could be set up for further inquiry. As Krause very pertinently observed:

[1] From the Division of Research, Milbank Memorial Fund.

[2] Which is composed of those states (and the District of Columbia) whose completeness of registration of deaths conformed to a standard set up by the Federal Bureau of the Census as early as 1900 and continuously afterward. It is used here because of the obvious desirability of a uniform mortality record for as large an unchanging area as possible over as long a period as possible. The states, other than New York, are Connecticut, Indiana, Maine, Massachusetts, Michigan, New Hampshire, New Jersey, Rhode Island and Vermont, and the District of Columbia.

Of course, what we want to know is whether these death returns actually or substantially reflect what is going on in tuberculosis in the country districts, not only in New York State but in the other states of the nation as well. If, under present conditions of environment and organized propaganda, the trend of tuberculosis is away from our cities and toward our rural sections, it is of enormous importance to discover the fact; as well as whether the country districts of agricultural states and sections are going the same way as those

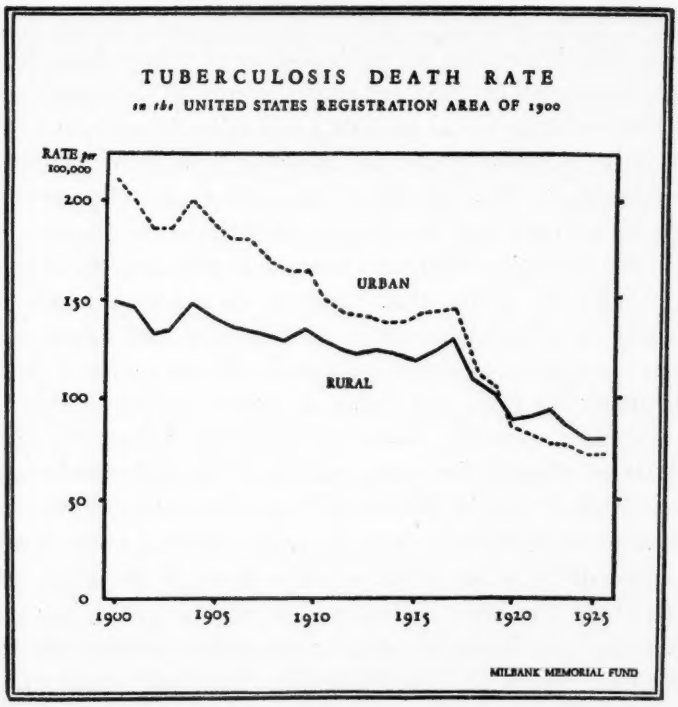

FIG. 1. Annual death-rates per 100,000 population from tuberculosis (all forms), as recorded in 1900–1926 for urban and rural parts of the "original" registration area. For the rates and sources of data used in this diagram, see note (2) of this paper.

of highly developed industry. Accurate information on these points should give us more exact testimony of the influence of social hygiene than we have ever had heretofore, and will make clearer the directions of future effort. If rural tuberculosis is really holding its own, or increasing, while that in the cities is retreating, the fact is *prima facie* evidence that the far-flung organizations of the cities are working to effect while rural laissez faire is paying the penalty of its inaction.

The student, however, is forced to face that arbitrary procedures in tabulation have crept into our official mortality statistics to such an

extent that no one except the tyro will regard them without considerable wariness or use them until he has inquired into the particular statistical procedures involved, entirely aside from any consideration of the accuracy and completeness of the original records. The effect of the specific statistical prodecure of tabulating tuberculosis deaths according to *place of death* upon the comparability of death-rates for different localities is a relevant instance (3) for the particular reason that many tuberculous persons die away from their usual place of residence in sanatoria and other institutions or in places where the environment is thought to be more favorable. Such official rates cannot be interpreted as indicating the mortality from the disease among the *population* of a locality, which is the datum desired, but only as the mortality occurring within the geographical boundaries of the locality, which is a rather useless piece of information.

EFFECT OF CORRECTING THE RECORDED RATES FOR RESIDENCE OF DECEDENTS

Two critical studies already have appeared that deal with this particular matter. Both have undertaken specifically to ascertain what the effect of a more accurate allocation of deaths would have upon urban and rural tuberculosis death-rates as officially recorded.

The first was a comprehensive and careful study by DePorte (4) on all tuberculosis deaths recorded in the State of New York during 1926. In this study the death certificates themselves were carefully examined for the last permanent residence of the decedent, the length of residence at the place where death occurred and the duration of illness. Deaths were reallocated to the place where the disease was contracted if that information was contained in the certificate. In instances in which this information was not available, then the facts as to length of residence in the place where the death occurred and the duration of the illness were taken into account. Reference may be made to the report on his study for details of procedure which cannot but impress the reader otherwise than as being reasonable and painstaking. The results of the scrutiny of the 10,076 deaths in New York State in 1926 are summarized in the following table which is extracted from DePorte's excellent paper:

DePorte's study contributes a number of interesting details relating to tuberculosis mortality in New York State, but, as he himself emphasizes in his conclusions, the important fact established by this study was, "that *the resident death-rate from tuberculosis of rural New York is lower*

Deaths from tuberculosis, all forms, by residence of decedent and recorded and resident death-rates in New York State during 1926

PLACE OF DEATH	POPULATION ESTIMATED AS OF JULY 1, 1926	TOTAL RECORDED DEATHS	RESIDENTS* OF					DEATH-RATES PER 100,000 POPULATION	
			New York City	Rest of State				Recorded	Resident
				Total	Urban	Rural	Institutional districts		
New York State	11,318,734	10,076	6,070	4,006	2,767	1,199	40	89.0	89.0
New York City	5,924,018	5,503	5,469	34	23	11		92.9	102.5
Rest of State	5,394,716	4,573	601	3,972	2,744	1,188	40	84.8	74.3
Urban	3,326,331	2,342	180	2,162	2,055	107		70.4	83.2
Rural	2,017,177	1,765	212	1,553	542	1,011		87.5	59.4
Institutional districts	51,208	466	209	257	147	70	40		

* Includes residents of other States and foreign countries and those whose residence was unknown or not stated.

Data from DePorte (4).

than the urban rate" for the year 1926. More specifically, he shows that the rural tuberculosis death-rate was actually two-thirds of the recorded rural rate while the urban tuberculosis death-rate was 18 per cent higher than the recorded death-rate.

The second study which appeared is by Miss Whitney (5), which also related to New York State and undertook to cover a period of eight years instead of only one year. The method of this study was "to discover from observation of the original death certificates themselves the usual place of residence of rural decedents and the time of their residence at the place of death." The results are summarized in the following table which is taken from her report:

Mortality from tuberculosis in rural New York State, 1917–1924

YEAR	DEATH-RATES PER 100,000 POPULATION	
	As recorded	As corrected by excluding deaths of nonresidents
1917	134.7	90.1
1918	127.0	85.8
1919	119.0	73.3
1920	117.8	68.4
1921	108.4	59.5
1922	106.7	58.8
1923	101.2	57.0
1924	94.2	48.9

Data from Whitney (5).

It should perhaps be emphasized that the scope of her study was quite different from that of DePorte in another important respect, namely, that whereas DePorte scrutinized all of the death certificates, Miss Whitney confined her study to the certificates filed in Albany from the *rural* sections only, and made no attempt to allocate to rural sections those deaths of rural residents which occurred in urban areas. Accordingly, we should expect that the corrected rates for rural areas as given by Miss Whitney would be lower than those given by DePorte, and they are. A comparison of the results obtained by the two studies is easy to make from DePorte's data. The 1926 rural rate, as corrected by Miss Whitney's method, would be 50.1 as against DePorte's rate of 59.4. It appears, therefore, that the rate corrected according to Miss Whitney's procedure is 16 per cent lower than the rate after more complete correction, and it may be regarded as probable that all of her rates for the years 1917–1924 are also considerably under the rates corrected by DePorte's method. The adequacy of her corrected rates in depicting the *course* of rural tuberculosis mortality in 1917–1924 is subject to the assumption, of course, that the proportion of rural residents dying of tuberculosis in towns and cities did not materially change during this period.

Both of these studies are extremely valuable in throwing light on the importance of taking into consideration the factor of residence in any effort to determine the death-rate from tuberculosis in a large and perhaps representative rural population. DePorte's study gives us the more complete information for a single year while Miss Whitney's study throws some light on the trend of the tuberculosis death-rate in rural areas for the comparatively short but important period 1917–1924.

TREND OF TUBERCULOSIS MORTALITY IN A RURAL AREA, 1900–1926

To utilize either of the methods employed by these investigators in correcting the record for a longer period of years would be an extremely laborious and expensive undertaking. It has occurred to us that, with their studies as a starting point, probably a fair approximation of the real trend of rural tuberculosis mortality over a considerable period could be arrived at by a somewhat different and less arduous method. This method is to select an area in New York State which has been and is essentially rural and whose recorded tuberculosis mortality would not seriously be affected by conditions that result in the inaccuracies already referred to.

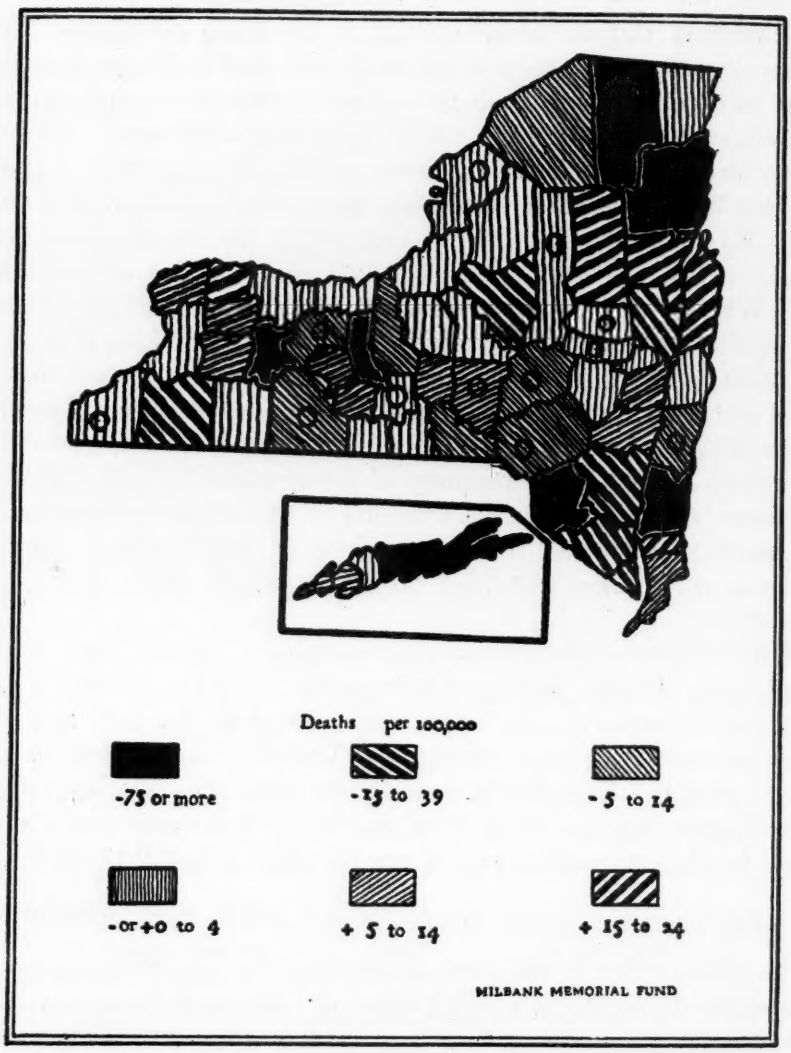

FIG. 2. Map of New York State, showing for each county the extent (in terms of rate per 100,000) to which the tuberculosis mortality in 1926 after correction for residence of decedents by DePorte (4) differed from the tuberculosis mortality as officially recorded. The counties marked by a circle are those included in the area selected for this study.

Obviously the value of this method is dependent upon the selection of the area to be used. In making this selection we had recourse first to DePorte's findings as to the recorded rates for individual counties, bearing in mind his caution that they are "not exact expressions of mortality from tuberculosis" and are "merely better approximation to actuality than are the recorded rates." Reference to the detailed figures given by DePorte will show that the corrected rates in New York City and 38 of the 57 counties were less than 15 per 100,000 above or below the recorded rate and that 21 were less than 5 per 100,000 above or below

TABLE 1

Death-rates per 100,000 from tuberculosis (all forms) as recorded, compared with rates as corrected by DePorte for residence of decedents for 12 specified counties in New York State, 1926

COUNTY	RECORDED	RESIDENT	DEVIATION OF RESIDENT FROM RECORDED RATE
Chenango	61.6	70.3	+8.7
Montgomery	87.0	90.2	+3.2
Chautauqua	56.6	56.6	
Jefferson	54.3	53.2	−1.1
Herkimer	78.9	77.4	−1.5
Fulton	36.7	34.6	−2.1
Tompkins	52.0	49.5	−2.5
Otsego	73.5	65.1	−8.4
Columbia	96.6	88.2	−8.4
Steuben	53.1	43.6	−9.5
Delaware	59.6	45.9	−13.7
Ontario	66.4	52.0	−14.4

Data from DePorte (4).

the recorded rate. It seems to us, however, that for our purpose certain further considerations of importance should be taken into account: (1) That since we are attempting to select a typical rural area, counties with cities of considerable size ought to be excluded; hence we excluded from consideration all counties which contained cities of 50,000 or more population. (2) That all counties containing state institutions, which might affect the tuberculosis mortality rate appreciably, or private tuberculosis sanatoria should be excluded. While the logic of this procedure is self-evident, its reasonableness is accentuated by the fact, as DePorte showed for 1926, that 46 per cent of the recorded deaths for tuberculosis in New York State (exclusive of New York City) occurred in institutions of some sort, that 31 per cent occurred in institutions

other than county tuberculosis hospitals and sanatoria, and that of this latter proportion the largest number occurred in Federal, State and private tuberculosis sanatoria, in state institutions and other institutions for tuberculosis. (3) That counties which had no county tuber-

TABLE 2

Death-rates per 100,000 from tuberculosis (all forms) as recorded for the rural population of New York State and for the entire population of 12 selected rural counties 1900–1926

YEAR	RURAL NEW YORK*	TWELVE COUNTIES†
1900	149.6	132.8
1901	151.1	130.6
1902	133.4	109.5
1903	135.3	115.8
1904	141.3	122.4
1905	145.6	123.3
1906	136.5	117.3
1907	140.9	120.5
1908	140.3	110.0
1909	136.4	108.1
1910	138.4	101.0
1911	140.1	110.9
1912	129.4	94.1
1913	128.1	91.1
1914	129.4	93.2
1915	126.7	91.6
1916	125.3	92.9
1917	131.4	94.7
1918	145.6	98.9
1919	135.7	81.8
1920	128.0	74.2
1921	113.7	74.1
1922	110.7	69.2
1923	108.6	71.7
1924	106.8	68.8
1925	95.1	63.0
1926	89.1	63.7

Data from Reports on Mortality Statistics of the Federal Bureau of the Census 1900–1915, 1916–1926 from the Annual Reports, New York State Department of Health, the figures for 1926 being provisional.

* Including towns and cities with populations less than 10,000.

† See text.

culosis sanatoria ought to be excluded because tuberculous residents are apt to go elsewhere for treatment and deaths of such persons frequently occurred outside of the boundaries of the counties concerned.

Applying the limitations dictated by these considerations, we had left twelve counties as follows: Chautauqua, Chenango, Columbia,

Delaware, Fulton, Herkimer, Jefferson, Montgomery, Ontario, Otsego, Steuben and Tompkins. The geographical location of these counties and their relation to the differences between the recorded and resident tuberculosis rates (as shown by DePorte) are depicted in the accompanying map (figure 2). It will be noted from table 1 that the resident rate in 1926 for each of these counties differed less than 15 per 100,000 from the recorded rate and that for 6 of these counties the difference was less

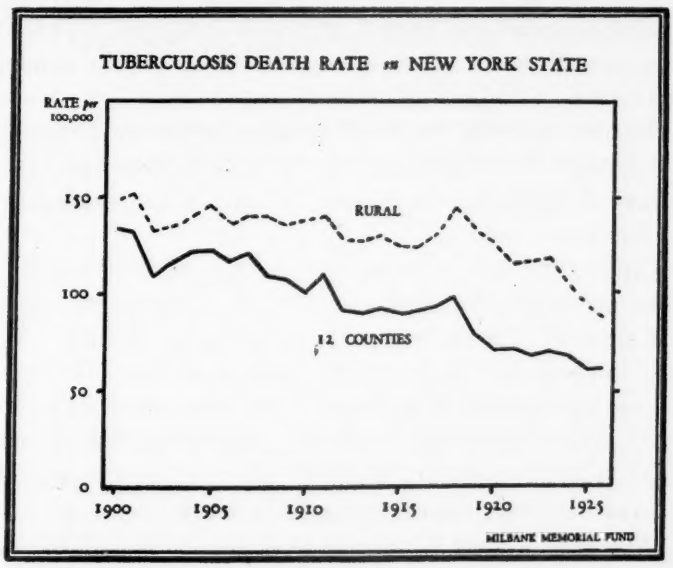

FIG. 3. Annual death-rates per 100,000 from tuberculosis (all forms), as recorded in 1900–1926 for the rural part of New York State (including towns and cities with populations less than 10,000) compared with those for the entire population of 12 counties selected as typically rural and as not affected by gross discrepancies between recorded and resident rates.

than 5 per 100,000. The total population of these counties, estimated as of 1926, was 742,177, and the tuberculosis death-rate as recorded was 63.7 for 1926 compared with 61.6 for the total rural population of New York State (that is, exclusive of cities having 10,000 or more inhabitants) as computed from DePorte's figures.[3] Thus, the recorded rate for the rural section represented by the 12 counties was only 2.1 per 100,000 above the resident tuberculosis rate for all the rural part of

[3] The limitation of 10,000 as a definition of a rural area, which is employed in this study, is not as satisfactory as a limitation of 2,500; necessity forced us to use it because the statistics were not available in the desired form for the whole period under observation.

New York State as defined above. It seemed to us, in view of the other considerations set forth, that we had selected a fairly representative section of New York State, which has been and is essentially rural and is not affected to a great extent by the factors which result in gross discrepancies between recorded and resident rates.

Using this territory in this manner, the deaths from tuberculosis as published by the Federal Bureau of the Census beginning with 1900 through 1915, and by the New York State Department of Health from 1916 on, were compiled and annual rates were computed. Table 2 gives these rates as well as the officially recorded rates for the rural part of New York State.

It will be observed that in the 27-year period the rate for this rural area was less than the recorded rate for rural New York State as defined above, thus corroborating the results of both of the studies to which reference has been made.

Now, if the 12 counties selected can be assumed to have been and to be a fairly representative rural section, the trend of its tuberculosis death-rate since 1900 is an interesting epidemiological fact. As shown graphically in figure 3 it was lower than the *recorded* rate in every one of the 27 years; but the difference between the two was less in 1900–1907 than at any subsequent period, indicating that up to 1908 correction for nonresident deaths would have had little effect upon the rate. In subsequent years, however, the difference between the two rates increased, at least until 1924. Thus it appears that the downward trend of the tuberculosis death-rate in a representative rural section has been greater and more consistent during the 27-year period than the officially recorded death-rate for rural New York indicates.

URBAN RATES CORRECTED FOR RESIDENCE

Now if the rural tuberculosis mortality rate as officially recorded is subject, in so great degree, to correction on account of residence, obviously the urban rate is also subject to correction. From DePorte's data, already given, the following summary is made for 1926:

LOCALITY	TUBERCULOSIS DEATH-RATE PER 100,000		PER CENT CHANGE RESULTING FROM CORRECTION
	As recorded	Corrected for residence	
New York City	92.9	102.5	+10.3
Other New York urban	70.4	83.2	+18.1

Corrections of both urban and rural rates thus are necessary before they can be compared.

Annual Rates for 10 Cities, 1914–1921 and 1926, Corrected for Residence

From data furnished by the Bureau of Vital Statistics, New York State Department of Health, and compiled under the supervision of the

TABLE 3

Death-rates per 100,000 from tuberculosis (all forms) in ten New York cities as officially recorded and as corrected for residence of decedent, 1914–1921 and 1926

YEAR	AS RECORDED*	CORRECTED FOR RESIDENCE OF DECEDENTS†	PER CENT CHANGE RESULTING FROM CORRECTION
1914	146.1	155.0	+6.7
1915	141.1	150.6	+6.7
1916	139.9	150.1	+7.3
1917	145.2	157.5	+8.5
1918	143.4	157.0	+9.5
1919	107.6	126.7	+17.8
1920	93.0	109.5	+17.7
1921	83.7	97.6	+16.6
1926	71.1	82.6	+16.2

* By Division of Vital Statistics, New York State Department of Health.

† For 1914–1921, data supplied by the late Doctor Otto R. Eichel, New York State Department of Health. For 1926, from data in DePorte's report (4).

late Dr. Otto R. Eichel, director of that bureau, we are able to compute the annual *resident* tuberculosis death-rates in 1914–1921 for a group of ten New York cities, as follows: Buffalo, Rochester, Albany, Binghamton, Niagara Falls, Schenectady, Syracuse, Troy, Utica and Yonkers. The procedure employed by Eichel[4] was essentially the same as that followed

[4] Dr. Eichel's statement of his procedure was as follows: "All the tuberculosis deaths in New York State (exclusive of New York City) were charged to the district in which the decedent resided when the disease was contracted as far as this could be determined from the death certificate. Those for whom no former residence was given were charged to the district in which the death occurred. Tuberculosis deaths in hospitals, sanatoria, etc., were allocated in the same manner. Tuberculosis deaths in state institutions were charged to the district of residence at the time of admission; deaths which could not be thus allocated were charged to the institution as a separate registration district and not included in the district in which the institution was situated."

The populations of state institutions were not included in the populations upon which the rates were computed. While DePorte employed some further refinements in method in his 1926 study, his general procedure was essentially similar to that of Eichel.

by DePorte with the exception that Eichel did not include deaths of residents of any of these ten cities which occurred in New York City. Since DePorte found that only 23 such deaths occurred in 1926, the consequences of this omission are not important. The annual tuberculosis death-rates for this group of ten cities, as officially recorded by the New York State Department of Health and as corrected for residence of decedents, are given in table 3. From DePorte's data the rate has been computed for these ten cities for 1926 also. It will be observed that the correction of the recorded rate is progressively greater in 1914–1919, a marked increase being shown in 1919 which has been fairly constant since then; in 1914–1918 the urban rate ought to have been from 6 to 10 per cent higher than it was recorded, and from 1919–1926 at least 16 per cent higher.

Estimated Annual Rates for Urban New York, 1900–1926

With all these data available to us and upon the assumption as to the significance of the rurality of the rate for 12 counties, it is possible to estimate the annual tuberculosis death-rates for the urban population of New York State for the entire period 1900–1926. In order to do this, however, a little arithmetic is necessary, as follows: After finding the annual differences between the rate for the 12 counties and the recorded rural rate for New York and, considering them as the net extent to which the recorded rate for rural New York ought to be corrected for residence, we can compute the number of deaths these differences in rates represent for the total rural population (as defined for purposes of this study). These computed numbers of deaths may then be added to the deaths recorded as occurring in urban New York (that is, cities having 10,000 or more population, including New York City). On the resulting totals urban death-rates, estimated as corrected for residence, may be computed (6). This procedure has been followed for each year and the results are given in table 4, in which are also shown the corrected rates for the ten cities for 1914–1921 (Eichel) and 1926 (DePorte). The estimated urban rates are somewhat higher than the rates for the ten cities in each of the years for which both are available, which is to be expected since New York City, whose tuberculosis death-rate is higher than that for the group of ten cities, is included. Our estimate of the total urban rate corrected for residence for 1926 (91.9) was checked against the actual corrected rate for the total urban area which DePorte's data afforded (97.2), and we find that our estimate is actually

and only about 5 per cent too low for this one year. The closeness of our approximation for this year, the fact that the two series for 1914–1921 behave in essentially the same way, and the conformity of our results

TABLE 4

Death-rates per 100,000 from tuberculosis (all forms) estimated as corrected for residence in urban New York State, 1900–1926 and corrected for residence in ten New York cities 1914–1921 and 1926

YEAR	URBAN NEW YORK AS ESTIMATED*	TEN CITIES†
1900	254	
1901	249	
1902	228	
1903	232	
1904	241	
1905	231	
1906	232	
1907	225	
1908	221	
1909	209	
1910	208	
1911	200	
1912	192	
1913	192	
1914	192	155
1915	186	151
1916	174	150
1917	179	158
1918	181	157
1919	155	127
1920	134	110
1921	110	98
1922	108	
1923	105	
1924	102	
1925	94	
1926	92	
1926	97‡	83

* Including New York City but excluding cities under 10,000 population.

† Buffalo, Rochester, Albany, Binghamton, Niagara Falls, Schenectady, Syracuse, Troy, Utica and Yonkers.

‡ Actual corrected rate for urban New York (including New York City but exclusive of cities under 10,000 population) as computed from DePorte's data (4).

with other and more generally known facts, lead us to the conclusion that the estimates of what the annual urban rates would be, had they been corrected for residence, are at least closer to the truth than the recorded rates.

COMPARISON OF THE COURSE OF TUBERCULOSIS MORTALITY FOR URBAN AND RURAL POPULATIONS

We are now able to make some comparisons of the course of the death-rates from tuberculosis for urban and rural populations in New York State that, it seems reasonable to believe, are much more accurate than the comparisons yielded by the officially recorded statistics.

The first comparison covers the limited but important period from 1914 through 1921 and in 1926, and is shown in table 5 and figure 4.

Two indications afforded by the foregoing comparison are extremely significant: (1) that the rural tuberculosis death-rate since 1914 has

TABLE 5

Death-rates per 100,000 from tuberculosis (all forms) for 12 selected rural counties and for 10 large cities in New York State 1914–1921 and 1926

YEAR	TWELVE COUNTIES*	TEN CITIES†	EXCESS OF URBAN OVER RURAL	
			Rate	Per cent
1914	93.2	155.0	62.8	67
1915	81.6	150.6	59.0	64
1916	92.9	150.1	57.2	62
1917	94.7	157.5	62.8	66
1918	98.9	157.0	58.1	58
1919	81.8	126.7	44.9	55
1920	74.2	109.5	35.3	48
1921	74.1	97.6	23.5	32
1926	63.7	82.6	18.9	30

* See text.

† Buffalo, Rochester, Albany, Binghamton, Niagara Falls, Schenectady, Syracuse, Troy, Utica and Yonkers. The rates have been corrected for residence of decedents.

been and still is (at least as late as 1926) lower than the urban rate, and (2) that the excess of the urban over the rural rate is not only actually but relatively much less since 1920 than it was prior to that year. Or, to put it conversely, the urban rate in the period 1914–1926 has declined much more rapidly than the rural. These indications are true if our primary assumption is correct, namely, that the rate for the 12 counties selected as typically rural is truly representative of the rural rate after correction for residence of decedents; the rate for the 10 cities may be accepted as not only typically urban but adequately corrected for residence.

The second comparison is of the trends in the rural and urban tuberculosis death-rates over a much larger period, 1900–1926. For this pur-

pose we use the annual rates for the 12 rural counties and the estimated annual urban rates which already have been described, as in table 6 and plotted in figure 5.

Thus, if our assumption as to the rurality of the rate for the 12 counties is a reasonable one and if our estimate of the corrected urban rate is approximately true, the foregoing comparison indicates (1) that throughout the entire period 1900–1926 the urban tuberculosis death-rate was higher than the rural rate and (2) that, whereas the urban rate was

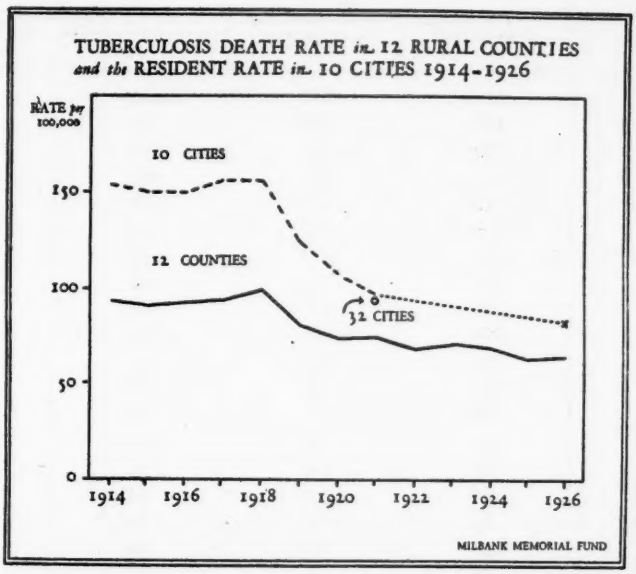

FIG. 4. Annual death-rates per 100,000 population from tuberculosis (all forms) 1914–1926 in 12 New York counties, selected as typically rural and as not affected by gross discrepancies between recorded and resident rates, compared with the annual *resident* rates in 10 large cities for 1914–1921 and 1926. The ten cities were Buffalo, Rochester, Syracuse, Albany, Binghamton, Niagara Falls, Schenectady, Troy, Utica and Yonkers. For 1921 the resident rate for 22 additional smaller cities is also shown.

nearly 100 per cent higher than the rural rate in 1900–1916 and about 85 per cent higher in 1916–1920, it has been about 50 per cent higher in 1921–1926. This considerable excess of urban tuberculosis mortality over rural corroborates the findings of DePorte for 1926 and of Miss Whitney for 1917–1924 and is directly contrary to the official figures since 1920. The difference between the urban and rural rates, whether it be that determined by DePorte for 1926 or that found by us for any one of the years 1920–1926, is too great to be explained by differences in the age distributions of urban and rural populations (7).

The same general result appears if the recorded tuberculosis death-rates are contrasted for urban and rural states. For example, let us take Massachusetts, with only 5.2 per cent of its population classified as rural, and Vermont with 68.8 per cent rural population in 1920. The

TABLE 6

Death-rates per 100,000 from tuberculosis (all forms) recorded for 12 selected rural counties in New York State, and estimated death-rates for urban New York as corrected for residence of decedents: 1900–1926

YEAR	TWELVE COUNTIES AS RECORDED*	URBAN NEW YORK AS ESTIMATED†	EXCESS OF URBAN OVER RURAL	
			Rate	Per cent
1900	133	254	121	91
1901	131	249	118	90
1902	110	228	118	107
1903	116	232	116	100
1904	122	241	119	98
1905	123	231	108	88
1906	117	232	115	98
1907	121	225	104	86
1908	110	221	111	101
1909	108	209	101	94
1910	101	208	107	106
1911	111	200	89	80
1912	94	192	98	104
1913	91	192	101	111
1914	93	192	99	106
1915	92	186	94	102
1916	93	174	81	87
1917	95	179	84	88
1918	99	181	82	83
1919	82	155	73	89
1920	74	134	60	81
1921	74	110	36	49
1922	69	108	39	57
1923	72	105	33	46
1924	69	102	33	48
1925	63	94	31	49
1926	64	92	28	44

* See footnote to table 1 and text.

† See text for method of making these estimates.

annual rates, which are easily available from the federal mortality reports, are plotted in figure 6. Although the differences between the graphs are not as large as those shown in figure 5—and obviously we should not expect them to be, since the urban and rural distinction is

not as sharp—the contrast is generally similar to and tends to confirm that shown for New York.

Finally, the figures arrived at in table 6 afford us a probably more accurate basis for comparing the *trends* of urban and rural mortality from tuberculosis than we have had heretofore in the officially recorded

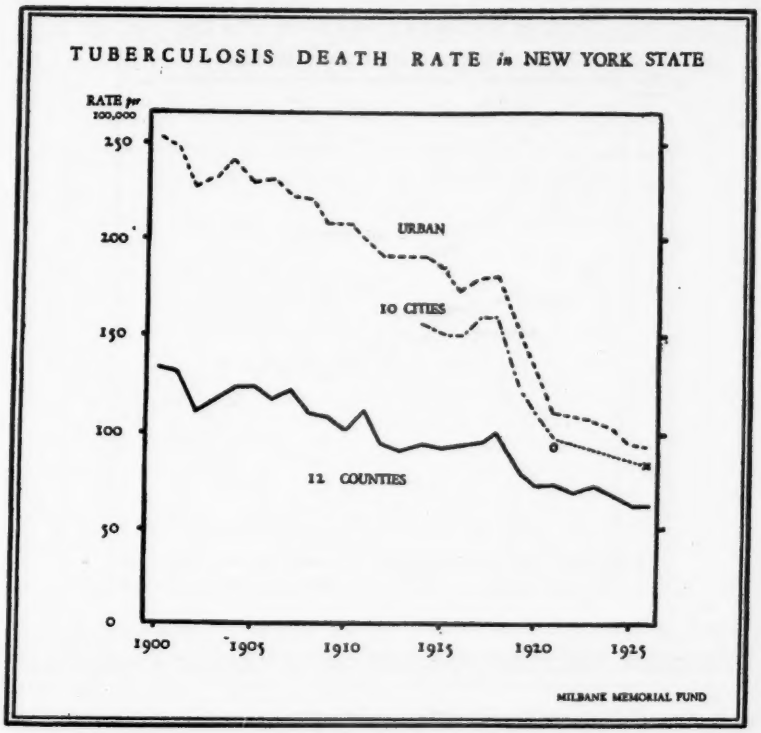

FIG. 5. Annual death-rates per 100,000 population from tuberculosis (all forms) 1900–1926 in 12 New York counties, selected as typically rural and as not affected by gross discrepancies between recorded and resident rates, compared (1) with annual rates estimated for the urban part of New York (including New York City) and (2) with annual resident rates in 10 large cities (exclusive of New York City) for 1914–1921 and 1926.

statistics. Although both urban and rural rates declined throughout the period 1900–1926, and although the urban rate was always in excess of the rural, the *relative* difference between the two does not tend to be constant, as the percentages in the last column show and as we have already observed. This means that, for the period as a whole, the *rate of decline* in one rate was greater than that in the other. The compari-

son of the trends will be more easily seen if the annual death-rates are plotted on a logarithmic ordinate scale and one graph is superimposed upon the other as in figure 7. The *rates of change* in the annual figures are thus made strictly comparable.

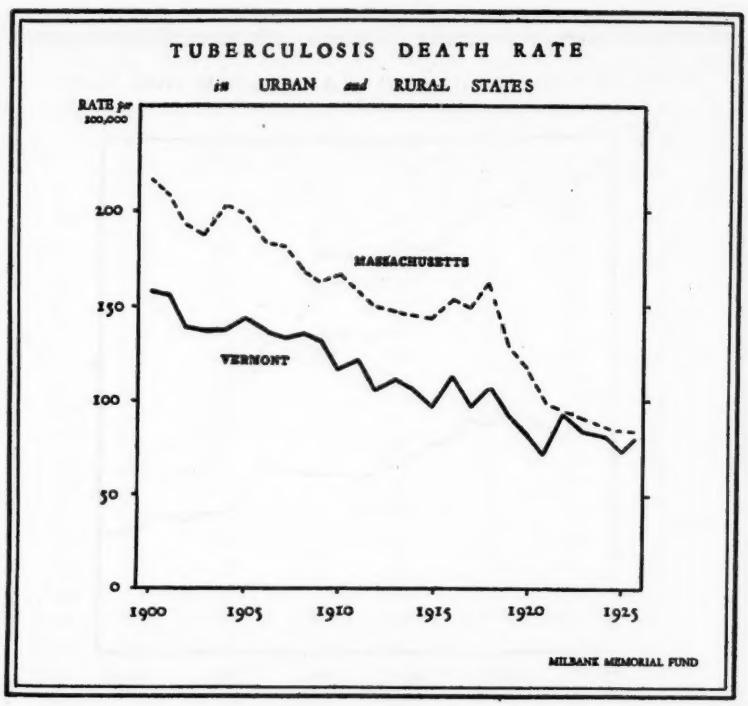

FIG. 6. Annual death-rates per 100,000 population for tuberculosis (all forms), as recorded in Massachusetts and Vermont, 1900–1926. The proportions of the populations in these states which were classified as "rural" in 1900, 1910 and 1920 are as follows:

	1900	*1910*	*1920*
Massachusetts	8.5	7.2	5.2
Vermont	77.9	72.2	68.8

SUMMARY

The indications yielded by this comparison may be summarized as follows:

1. The *trend* of the rural tuberculosis death-rate was essentially identical with the urban tuberculosis death-rate during the period 1900–1915. Although the urban rate maintained itself at a ratio to the rural rate of about 2 to 1, the proportionate decline was approximately the same in both populations.

2. Immediately subsequent to the depression of 1914–1915 and in the influenza epidemic of 1918 a rise in mortality attributed to tuberculosis occurred which was followed by a sharp drop in the death-rate from the disease in 1919–1921. In these three years the urban rate declined more rapidly than the rural. Since then both rates have been declining somewhat more rapidly than in the period 1900–1916.

It is not the purpose of this paper to attempt an interpretation of this comparison. Without more detailed statistics of the mortality and data on the relevant conditions we can go no further than to summarize

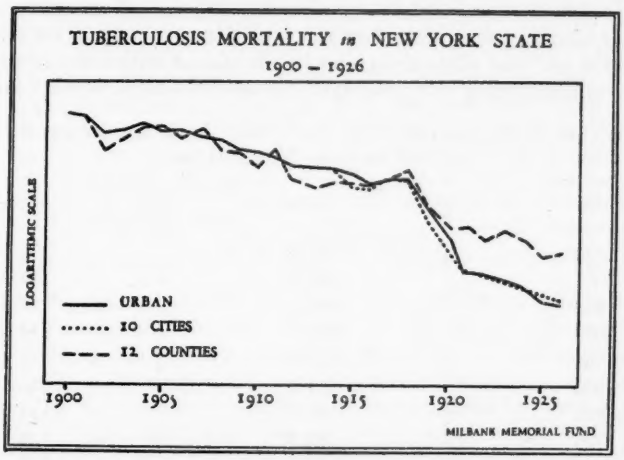

FIG. 7. Same as fig. 5, but plotted on a logarithmic ordinate scale, with the contrasted rates for the 12 counties and the estimated urban superimposed at 1900 and the contrasted rates for the estimated urban and the 10 cities superimposed for 1914, in order to compare the *slope* of the graphs.

our findings as follows: The *net* effect of the interplay of various factors upon the tuberculosis death-rate in urban and rural situations was approximately the same during the period from 1900 until the World War, but since then the forces favoring a decline have been somewhat more powerful in cities than in country districts.

Acknowledgments are made to the Bureau of Vital Statistics, New York State Department of Health, for tabulations especially made for the Milbank Memorial Fund, and to the Office of Statistical Investigations, United States Public Health Service, for use of certain data in its files. I am indebted also to Doctor A. C. Burnham, of the State Charities Aid Association, New York City, who read the first draft of the manuscript of this study and made helpful suggestions.

REFERENCES AND NOTES

(1) KRAUSE, A. K.: "Urban and Rural Trends of Tuberculosis Mortality Contrasted." Editorial in *American Review of Tuberculosis*, March, 1926 (xiii: 285–291).

(2) The mortality data were extracted from the mortality reports of the Federal Bureau of the Census.

Unfortunately it was not practicable to utilize exactly the same definitions of "rural" and "urban" throughout the period. For the years 1900–1909 "urban" included the population living and deaths occurring in cities having 8,000 or more inhabitants, and for 1910 and later in cities having 10,000 or more inhabitants. "Rural" includes all other parts of the area under consideration. The latest intercensal estimates of urban and rural populations issued by the Bureau of the Census were used wherever available, but estimates were made by straight-line interpolation for 1906–1909, and 1911–1916, the results being checked against the estimates of the total population of this area as published by the Bureau of the Census. Since urban and rural tuberculosis rates for the original registration area from 1900 on have not appeared in the literature, they are given in the following table:

Death-rates per 100,000 from tuberculosis (all forms) in the original registration area of 1900, excluding New York State

YEAR	URBAN	RURAL
1900	216.9	155.1
1901	206.9	149.3
1902	192.1	137.5
1903	193.7	139.2
1904	205.8	152.1
1905	194.6	146.1
1906	186.8	141.1
1907	185.0	138.1
1908	174.8	135.5
1909	169.6	131.8
1910	169.6	138.2
1911	155.1	132.6
1912	148.2	127.2
1913	146.7	125.9
1914	143.4	127.9
1915	143.8	126.1
1916	147.2	123.3
1917	148.4	126.5
1918	148.6	134.2
1919	118.8	113.2
1920	107.0	106.3
1921	89.2	92.1
1922	84.2	94.7
1923	80.8	97.6
1924	78.3	89.0
1925	73.8	82.5
1926	75.0	83.2

Data from Reports on Mortality Statistics of the Federal Bureau of the Census 1900–1926.

(3) The weakness of official mortality statistics arising from the method of recording deaths according to place of death is of course recognized by the Federal Bureau of the Census. In fact, in its annual report on mortality statistics for 1918 it published a reallocation of deaths from all causes for each county and city in the registration area. It may be interesting to note that according to the procedure of reallocation employed in that report the death-rate for urban New York (including New York City) would have been 2 per cent lower than that officially recorded and for rural New York 4 per cent higher. The definition of residence used—"place where a person usually sleeps"—is manifestly unsatisfactory for proper allocation of tuberculosis deaths. Note, for example, the result that the gross death-rate for Denver is reduced only 9 per cent by this method.

(4) DEPORTE, J. V.: "Recorded and Resident Death-Rates from Tuberculosis in New York State in 1926." *American Review of Tuberculosis*, June, 1928 (xvii: 634–662).

(5) WHITNEY, JESSAMINE S.: "Study of Urban and Rural Tuberculosis Death Rates in New York State." American Journal of Public Health, August, 1928 (xviii: 978–984).

(6) For example, the difference in the 1926 tuberculosis death-rates for rural New York (as defined for the purposes of this study) and for the 12 selected counties was 25.4 per 100,000. Now, since by the formula for computing specific death-rates $= \left(\frac{\text{Deaths} \times 100{,}000}{\text{Population}}\right)$ the number of deaths can be found when the rate and population are known $\left(\frac{\text{Population} \times \text{Rate}}{100{,}000}\right)$, the number of deaths represented by this difference in rates (25.4) is 656. The rate per 100,000 urban population for these 656 deaths is then computed as 7.6 and added to the recorded rate, which is 84.3, making 91.9 as the estimated urban rate corrected for residence.

(7) If the New York State urban and rural tuberculosis official death-rates for 1920, for instance, are standardized for age, the difference in the two rates due to differences in the age distributions of urban and rural populations is only 1.3 per 100,000. In standardizing the rates, the official federal age specific rates for the entire state were used. The age-groupings used were 0–4, 5–9, 10–14, 15–19, 20–44, and 45 and over, which were the most detailed available for urban and rural populations. The reader is referred to Pearl's *Medical Biometry and Statistics* (pp. 198–202) for procedure.

The change in the age distribution of urban and rural populations in New York from 1910 to 1920, while interesting from some other point of view, was not sufficient to affect materially the difference between the standardized tuberculosis death-rates for urban and rural areas, as the following table, compiled from the 1920 census reports clearly shows:

Age distribution of urban and rural population of New York State compared for 1910 and 1920

AGE-GROUPS	URBAN		RURAL	
	1910	1920	1910	1920
All ages	100.0	100.0	100.0	100.0
– 5	10.1	9.8	8.9	9.2
5– 9	8.9	9.4	8.7	9.3
10–14	8.6	8.6	8.6	9.0
15–19	9.4	7.9	8.5	7.6
20–44	44.5	43.2	36.5	34.3
45 and over	18.3	20.9	28.7	30.5

Comparable age distributions are not available for 1900, but I think we can safely assume that the great difference in the urban and rural tuberculosis death-rates are not affected to a considerable extent by differences in the age distributions of the population concerned.

It is equally apparent that the trend of either the urban or the rural rates would not be affected sufficiently by changes in the age distribution of the populations to modify the general indications later commented upon in this paper.

EXPERIMENTS ON THE FILTERABILITY OF THE GRANULAR PHASE OF THE TUBERCLE BACILLUS[1]

RALPH R. MELLON AND ELIZABETH L. JOST

The chief reason for our report on this subject at the present time lies in the categorical nature of the results obtained within the limitations imposed by the technique employed. We refer now to the production, by means of filtrates of tuberculous materials, of the classical form of tuberculosis with the presence of numerous acid-fast bacilli, which could be isolated from these lesions and recognized as typical tubercle bacilli. Furthermore, after being recovered, these latter bacilli readily produced classical tuberculosis when reinjected into other animals. Despite the many published papers on the subject, very rarely do we find one claiming to satisfy all of these postulates.

A further reason for publication is the fact that these definitely positive results have been obtained solely with tuberculous material very rich in the so called granular phase of the tubercle bacillus. Although it cannot be said with certainty that the rest of our material contained no granules, the granules certainly were not conspicuous, and in most instances they were not even noticeable. This fact strengthens the possibility that the forms actually passing the filter were either the granules as we see them, or something still smaller that possibly may be derived from the granules. This aspect of the situation we shall discuss more at length presently.

And, finally, an additional reason for this report is to give the whole subject its proper setting; that is, as an aspect of the conception that bacteria have true life-cycles, with all that this may imply in their physiopathology. In the light of this conception our relatively few experiments have yielded results sufficiently definitive to furnish a clue perhaps to the inconstancy of the results of filtration experiments with this microorganism.

Following the claims of Fontes (1910) that he had accomplished successful filtration of the tubercle bacillus through clay filters there has in

[1] From the Institute of Pathology, Western Pennsylvania Hospital, Pittsburgh, Pennsylvania.

the past five years grown up a voluminous literature on the subject. This has come largely from the French "school," the dominant note sounded being a confirmatory one, with but relatively few dissenters from Fontes's point of view.

On account of our own work over a number of years on the biology and the life-history of bacteria we have been sympathetic with this point of view. On the other hand, an impartial examination of the literature gives us distinctly the impression that the claims usually made have been out of all proportion to the evidence on which they were based. Certainly the exceptions are exceedingly rare.

The evidence of Fontes in his original paper can be briefly summed up by his finding gram-positive granules included in round cells of the lymph nodes of animals which had been inoculated with supposedly virus-containing filtrates. Transfer of these organs to fresh guinea pigs yielded, after three to six months, very scanty acid-fast bacilli in the lymph nodes and lungs. No definite lesions of organic tuberculosis were demonstrated, the only changes designated as lesions consisting of congestion in the lungs. The considerable majority of the large number of French papers on the subject have gone little further than this. Some, it is true, speak of atypical tuberculous lesions or tubercle-like reactions in the lymph nodes and some of the organs; and Arloing and his co-workers (1926) stress considerably the cachexia which is developed in many of the animals in which finally only acid-fast bacilli are found.

But Montemartini (1925) reports negative results, believing that the tissue reaction caused by the injection of relatively undiluted filtrates really are of a toxic nature. Fessler (1926) and Petroff (1928) and others also report negative results. Some of these workers are even much inclined to attribute an occasional positive result to spontaneous tuberculosis. However, before the claims become distinctly convincing to the impartial observer it will be necessary to produce some of the recognized forms of classical tuberculosis; this, too, under conditions that rule out the possibility of spontaneous tuberculosis. The lesions produced must be unmistakably those recognized and caused by the tubercle bacillus, and this microörganism will, of necessity, have to be isolated from these lesions and be capable of reproducing the lesions in another series of experimental animals. As we have mentioned before, the reports of this sort are conspicuous by their rarity.[2]

[2] We desire it to be clearly understood that by advocating such categorical criteria at this time we do not wish to exclude the possibility that filtrates may give rise to lesions not now

The only paper that we have discovered in the literature, previous to the one published by ourselves in 1927 reporting a *bona fide* result from the filtrate of tuberculous material, is the one of Vaudremer and Durand (1924). Their paper is highly significant on account of the large number of the above postulates that it satisfies. These observers claim to have cultivated the typical bacillus of Koch from filtrates of the injected animal's pus. Vaudremer (1922) claims also to have filtered cultures of the tubercle bacillus which yielded non-acid-fast mycelioid forms that gave rise to acid-fast granules. The mycelioid forms, when injected into animals, set up a polyadenitis. The acid-fast granules originating apparently from the mycelioid forms in the animals, when they were reinjected into guinea pigs, produced a tissue eschar, which, however, did not have the characteristics of typical tuberculosis. The filtrates containing these forms were also injected into guinea pigs, and after an interval of some days the heart-blood was found to contain a positive culture of the mycelioid forms and acid-fast bacilli. Vaudremer and Durand give no further report of the fate of these particular forms or whether they were able to grow them for several generations. Later (1927), Togounoff (17), inoculating guinea pigs with filtrates of many cultures and of several tuberculous sputa, had from the latter an interesting result. The cachectic animal was killed after four and one-half months. The autopsy revealed two caseous nodules, which histologically showed tuberculous granuloma. Culturing was negative. Inoculation into a second guinea pig provoked little more than a nodule at the site of injection. No pathological change was developed by passage into a third animal.

More recently, Sweany (1928) has published highly interesting results, dealing with the filtrates of granular material from an enlarged but histologically nontuberculous spleen of an injected guinea pig. He was able to isolate with some difficulty a non-acid-fast diphtheroid bacillus from this spleen. A single passage of this culture into another animal developed an atypical tuberculosis, while a second serial passage de-

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recognized as characteristic for tuberculosis. Indeed, the biological differences which we have predicted for filtrates in general would predispose us favorably to such a view.

Nevertheless, until more is known about the life-cycle of this microörganism, and before we can reproduce such lesions with filtrates derived from *cultures*, with the cultivation perhaps of the filterable elements, it seems desirable to adhere to the above conventional criteria. If we are first able to reproduce some form of classical tuberculosis—and many aspects of this are atypical—we can then proceed with more certainty to the nonspecific cachexia of Arloing (*loc. cit.*) and his associates.

veloped typical or classical lesions of the disease. Sweany's results, together with those of Vaudremer and Durand, and Togounoff, have a pertinent bearing on many indeterminate tuberculous manifestations. There is good reason to believe that clinically we have numerous examples of these, but, until the life-cycle of the microörganism can be worked out with more certainty in culture, we cannot speak very definitely from the experimental standpoint. To this aspect of the subject we shall refer presently.

EXPERIMENTAL

Technique: The tuberculous material was autolyzed at 37°C. for 72 hours and first filtered through a mashed paper filter in a Buchner funnel. It was then passed through a Berkefeld-N bougie that had previously been tested against a culture of *Staphylococcus albus*. The filtrate itself was then incubated for 18 hours at 37°C. for growth. In some instances it was kept at 20° to 24°C. or in the ice-chest for several days to a week before inoculation.

In our first published positive results (1927) there was included an inoculation variable which it was impossible to evaluate at the time, and for that reason it was not mentioned specifically. This involves injection with the filtrate of a living, but nonpathogenic, or at best, very feebly pathogenic microörganism. The ground for its employment in this connection can be found by reference to our published studies on the positive inoculations that we obtained with filtrates of fusiform bacilli and diphtheroids (1926). Our experience with filterable or the gonidial phases of microörganisms has indicated to us rather definitely that they are physiologically and biologically different from the antecedent phase from which they are derived. One of the chief differences lies in their germinative capacity; that is, they may only germinate under conditions quite different from the so called normal phase of the microörganism. This consideration has been quite a fundamental one in all our studies of the life-cycles of microörganisms and is not confined purely to their filterable phases. The potentialities of the involution forms, so called, constituted, in fact, the rock on which we split with traditional views many years ago.

This living strain of microörganisms, which is injected concomitantly with the filtrate, we will designate as *C46*. Although its suggested rôle in this connection is not stated as a fact, we were under the impression that it facilitated the germination of the filterable form *in vivo*. On the

assumption that this is true, we have as yet no definite knowledge of the mechanism of this action. It is conceivable, of course, that there may be some symbiotic relationship between the microörganisms and the virus, or the action may be quite nonspecific, acting merely as an irritant to the body cells in the same way that inert substances are known to facilitate "takes" in tumor experiments with animals.

The positive results coming from our most recent experiments were concerned with material having its origin in the lung of a patient suffering from a pulmonary miliary tuberculosis. Direct examination of this material revealed very granular bacilli, while the stained sections showed an occasional bacillus and very numerous granules, a large proportion of which were intracellular. The bougie used for the filtration has been repeatedly controlled with other microörganisms. In this instance the filtered material was incubated over night at 37°C., and kept at room temperature for three weeks before its inoculation into 4 guinea pigs. Each of these animals of approximately equal weight was given 5 to 7 cc. of the filtrate intraperitoneally and approximately 1 cc. subcutaneously. After 8 months, guinea pig 36 died of an infection of pneumococcus and a gram-negative paratyphoid-like bacillus. There was no definite evidence of tuberculosis. The lymph nodes appeared normal except for the tracheobronchials, which were enlarged but not sclerotic.

In the second guinea pig, no. 39, the lymph nodes were hyperplastic, but showed definite circumscribed epithelioid areas indistinguishable from such areas in known tuberculosis of the guinea pig. The same changes were found in the spleen but without noteworthy change in the follicles. Nearer the capsule there was one rather large epithelioid granulomatous area. The lungs showed marked evidence of atelectasis, and scattered in the parenchyma were a few granulomatous structures indistinguishable from tubercle, although they were not markedly epithelioid, and did not have giant cells. Direct examination of the tracheobronchial, mesenteric, and inguinal lymph nodes for acid-fast bacilli was negative. Week-old cultures were negative.

The third animal, guinea pig 38, received, in addition to the filtrate, an injection of the C46 strain. After 7 months the animal was killed. Grossly, the autopsy showed nothing of note except slight enlargement of the inguinal lymph nodes. Direct smear examination of the various lymph nodes was negative. The spleen showed an apparent increase of the number of Malpighian bodies, while about the periphery of many of them was a moderate epithelioid change. Some of the germ-centres

had a distinctly epithelioid core, and there were a number of multinucleated epithelioid giant cells. They were not, however, perfectly characteristic for the Langhans type, the nuclei being grouped more as a cluster or rosette, yet their matrix appeared of a homogeneous nature. The lungs were negative, while the lymph nodes showed only nonspecific hyperplastic changes.

The fourth guinea pig, no. 37, was injected the same as the previous one and was killed after a period of seven and one-half months. At autopsy, the inoculation site was negative and the inguinal lymph nodes normal. The mesenteric and retroperitoneal lymph nodes were very much enlarged and markedly hardened. The same thing was true for the tracheobronchial lymph nodes, but, in addition, a small portion of one appeared caseous. The spleen was slightly enlarged and the other organs normal in the gross. Direct examination of the mesenteric and retroperitoneal lymph nodes showed slender acid-fast bacilli; many of them were granular. The same type of microörganism was found in the caseous material of the tracheobronchial lymph node. Histologically, these enlarged and hardened lymph nodes showed a fibrous type of tuberculosis. The normal architecture of the lymph node was destroyed, and the pathological process was characterized by relatively few epithelioid tubercles but no distinct evidence of caseation. Giant cells and hyaline fibrous connective tissue were much in evidence. In one lymph node there was a definite tubercle, showing a necrobiotic focus. The lungs showed nothing of note. As a whole, these changes would be said to be perfectly characteristic for this type of tuberculosis.

Two animals were inoculated with the ground spleen and two with ground lymph nodes of guinea pig 37. All four showed, within a month, marked enlargement and hardening of the inguinal lymph nodes at the site of the injection. These broke down and showed numerous acid-fast bacilli. One animal lived for thirteen weeks and the other three for sixteen, all dying with typical lesions of generalized tuberculosis, although the microörganism was apparently not very virulent. A typical tubercle bacillus was isolated from the lymph nodes of the original guinea pig, which, on inoculation into guinea pigs, produced classical tuberculosis.

ANALYSIS

It is clear that the first guinea pig of this series died of a nontuberculous infection, and from the standpoint of tuberculosis could be said to

be essentially negative. It had not received any injection of C46 with the filtrate. Although guinea pig 39 did not receive any injection of C46, it showed slight but rather definite epithelioid granulations in the lungs. Guinea pig 38, which received an injection of C46, showed lesions that were limited to the spleen. They consisted of rather striking annular epithelioid thickenings about the Malpighian bodies, as well as occasional tubercle-like granulations of similar tissue in the pulp. (See figures 1 and 2.) The animals can only be viewed as suggestively tuberculous, owing to the similarity of such lesions to those produced by a paratyphoid-like infection found in some of our animals, and to which we will refer presently. Guinea pig 37, on the other hand, also receiving C46 in addition to the filtrate, showed a widespread granular tuberculosis, absolutely definite in character, with subsequent inoculation results and positive cultures; in short, everything in accord with the most rigid criteria.

It is clear, then, that there is some question as to the action of the C46 strain in facilitating the development of tuberculosis. It should be said, however, in this connection, that the microörganism, when given to these animals, was quite avirulent in contrast to this condition at an earlier period when it produced moderate pathogenic effects. It should be stated definitely, though, that a careful pathological examination of the lymph nodes of at least a dozen animals that had been injected with this strain in its low virulent state never revealed changes even suggestive of tuberculosis. The changes produced here, then, cannot be referred in any direct way to the action of this microörganism.

The experimental details in connection with our original preliminary publication on the filtration of tubercle bacilli are as follows: The source of the material was a sputum which contained myriads of isolated, deeply-staining, acid-fast tubercle granules, along with markedly granular tubercle bacilli. When inoculated into a guinea pig, this sputum caused definite generalized tuberculosis in six weeks. An animal injected with the filtrate of this first specimen that had been autolyzed died of pneumonia in four weeks with no other obvious pathological changes. The second specimen was filtered in two lots and inoculated into two animals, nos. 790 and 791. The inoculation technique differed in no essential particular from that already detailed with the other series of animals except for the slight virulence of the accompanying symbiotic (?) bacillus.

After receiving the inoculations, no. 790 gained steadily in weight with good condition for eight months when it had a litter of young and

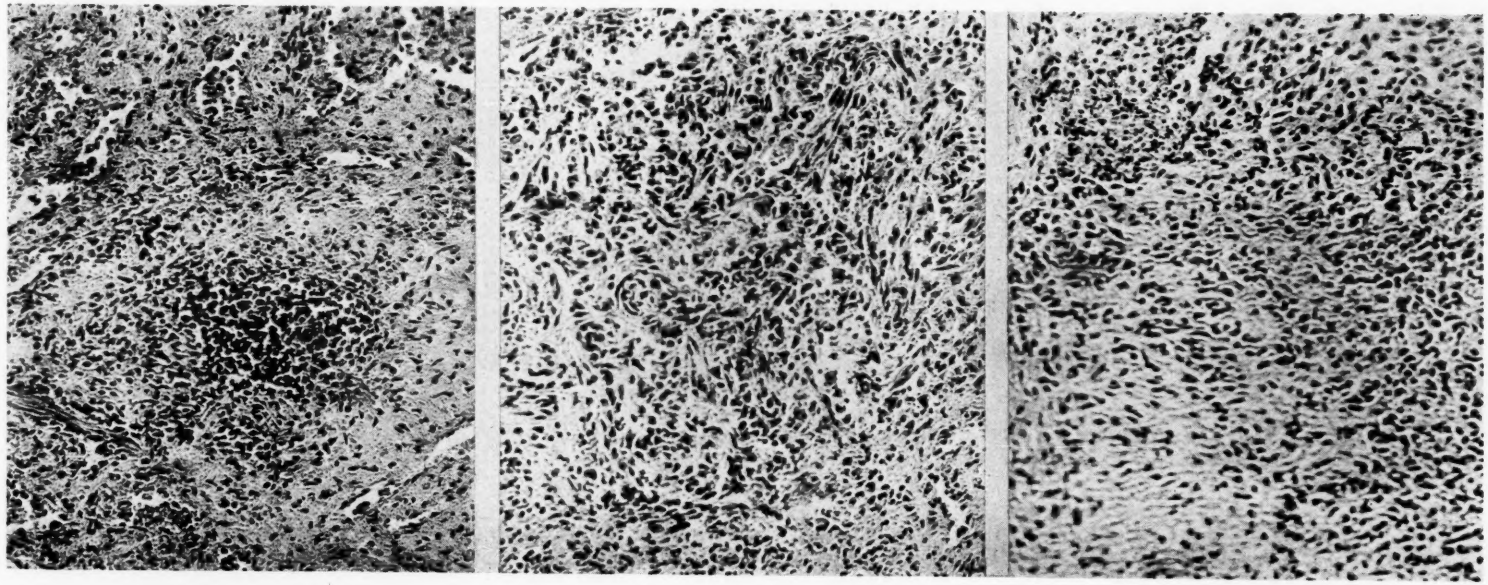

FIG. 1 FIG. 2 FIG. 3

FIG. 1. Shows annular hyalinized epithelioid formations at the periphery of Malphigian bodies in guinea pig's spleen. × 150.

FIG. 2. A tubercle-like granulation in guinea pig's spleen, smears of which contained a few acid-fast bacilli, but the lesion was caused presumably by virulent paratyphoid-like microörganisms which were quite numerous. × 275.

FIG. 3. A very cellular granulomatous lesion caused by a filtrate of granular tuberculous material. Early softening indicated by small collection of pyknotic nuclei in the upper part of the figure. ×275.

died. No changes of note were found in any of the organs and no acid-fast bacilli in the numerous smears made of the mesenteric, inguinal, and tracheobronchial lymph nodes. The third animal, no. 791, received an initial intraperitoneal injection of 8.5 cc. as against 6 cc. for guinea pig 790. The initial subcutaneous injection for no. 791 was 0.5 cc., and for guinea pig 790, 3 cc. Three weeks after the filtrate injection, a subcutaneous inoculation of C46 was given guinea pig 791. It gained weight and appeared healthy for eight months, when it died. There was nothing of note at the site of inoculation and the superficial lymph nodes were normal except for a conspicuous enlargement of the right axillary.

The other changes were essentially the same as those detailed for the conspicuously positive animal of the other series. The only exception in this case, perhaps, was the still more widespread tuberculosis in the liver and lungs, which were quite heavily involved. In guinea pig 791 the histological changes in the lymph nodes were rather reminiscent of lymphogranulomatous changes, in that the reaction, which was very cellular, obliterated entirely the normal architecture of the lymph node. (See figure 3.) But in some of the lymph nodes the lesions showed a marked destructive character, caseation being prominent. The microorganism was isolated from these lymph nodes as a typical tubercle bacillus which produced generalized tuberculosis when inoculated into a second series of guinea pigs.

Of a total of 37 guinea pigs injected with filtrates from various tuberculous sources, 13 animals showed completely negative findings. In 8 the cause of death was definitely identified as pneumonia or a paratyphoid-like gram-negative bacillus.[3] Two died of cachexia, but showed no acid-fast bacilli in their lymph nodes, while two more died of cachexia and did show acid-fast bacilli or granules in the lymph nodes. Two others died of classical tuberculosis. Two more guinea pigs exhibited in one or more lymph nodes or other organs a moderate involvement indistinguishable from known tuberculous lesions. In these two the

[3] It is well enough known, but too often unappreciated, that in guinea pigs there is a paratyphoid-like bacillus, producing necrobiotic lesions often closely resembling true tubercles. In fact, during this series of experiments we had a small epidemic of this infection, which in some animals gave gross lesions looking in most respects like true tubercles. Although usually necrobiotic, they may be entirely epithelioid, and, with a reaction about the same as is characteristic for tubercle, they are frequently indistinguishable. We have seen similar true tubercle lesions in guinea pigs of this necrobiotic character. The fact constitutes an additional warning for those who would conclude as to the origin of filtrate lesions on any but categorical evidence.

diagnosis was not confirmed by culture or subsequent inoculation. Three others showed pathological changes suggestive of tubercle but not conclusive, while the five remaining ones showed acid-fast bacilli in the lymph nodes, but without any definite pathological change characteristic of tuberculosis. Cooper and Petroff (1928) have examined a number of normal animals in this respect, and find acid-fast bacilli in the lymph nodes of about 33 per cent of those studied. Such findings abrogate quite completely evidence for tuberculosis based on practically nothing else than the finding of acid-fast bacilli.

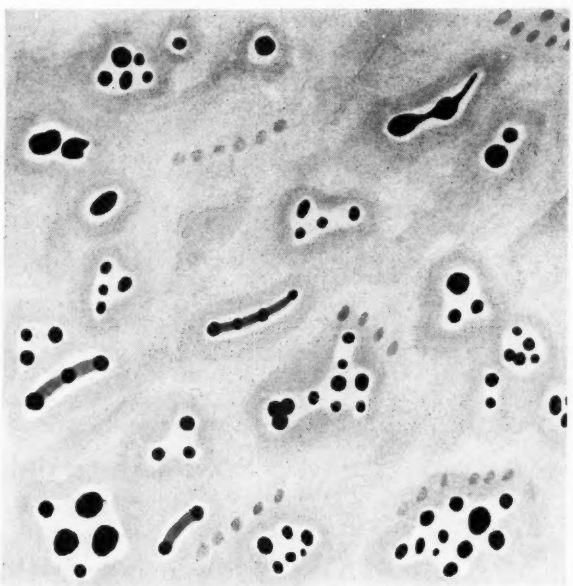

FIG. 4. A composite of types of acid-fast forms predominating in granular tuberculous material. Diagrammatic.

DISCUSSION

We consider it rather pertinent that the only positive results that we have obtained have come from material that was very rich in granules. All other experiments we have either classed as negative or have not felt sufficiently confident to designate them as definitely tuberculous. These granules have usually been of the type that stain bluish-red with carbol-fuchsin and may be found at the end of the bacillus and sometimes in its body, or they may be found apparently free, either singly or in groups. (Figure 4.)

From the standpoint of filtration we have never been satisfied that it was necessarily these granules themselves that passed through the filter. The reason for this position has had to do with experiences dealing with filterable phases of other microörganisms, on which we have reported in our *Studies in Microbic Heredity* (1926). We have felt indeed, that the actual filterable forms might be much smaller than these and might even be non-acid-fast. Accordingly, it was of considerable interest to us to observe the studies in the life history of the tubercle bacillus as at present being conducted by Dr. Morton C. Kahn[4] of Cornell University Medical College.

He has indicated that the type of granule that we have described here can, under the microscope, be seen to split into a number of very minute non-acid-fast granules, which have the capacity to regenerate themselves again to the bacillary form of the tubercle bacillus. Therefore, it seems not unlikely that, in accordance with our preconceptions on the matter, it is these smaller non-acid-fast granules that actually pass the filter. These preconceptions were based on the observation that with certain granular diphtheroids it was the intergranular gram-negative substance that formed the *Anlage* for the development of the filterable spore-like gonidia. We (1919, 1926) showed that when these bodies were not developed the microörganisms themselves were not filterable. These forms developed as minute spore-like bodies between the more deeply staining polar and intermediate granules of the diphtheroid microörganism. When inoculated into animals, under suitable conditions, they gave rise to the fusiform type of microörganism, producing lesions characteristic of this group.

From the standpoint of filtration technique it is, of course, very well known that many of the pores in even small filters are more than sufficiently adequate to permit the passage of ordinary-sized bacteria. Yet we have no sufficiently good evidence that the tubercle bacillus especially is capable of passing a Berkefeld-N filter, unless previously the walls of these pores have been so prepared as to prevent the adhesion of the microorganism to them. This point, we feel, is of very much greater importance than any considerations of electrical potential difference. It is probable that the large volume of media employed by Cooper and Petroff in their

[4] Personal communication. See also Kahn and Torrey: The Developmental Cycle of the Tubercle Bacillus as Revealed by Single-Cell Studies, AMERICAN REVIEW OF TUBERCULOSIS, December, 1928, xviii, 815.

work produced these conditions. In this connection it would have been of interest in the interpretation of their single positive result with sputum to know whether it contained an appreciable number of granules. Strictly speaking, any filtration technique is perhaps open to question, but, if all known controls are introduced, we believe the evidence strongly favors the position that the filtration results are as they appear.

In this connection it is of interest that tuberculosis developing from the filtrates is usually much delayed, and the tissue reaction is of the low-grade type associated with diminished virulence. The relation of virulence to phase changes in a microörganism's life history is well known. Moreover, the capricious germinative capacity of different phases of a microörganism, especially the filterable phases, is a fundamental consideration on which their newer biology has been built.

As Petroff has shown, the nature of the tissue reaction may be in part a function of the number of microörganisms injected. On the other hand, the observations of Togounoff (1927) indicate clearly that the low virulence of the initial infection (17) from filtrates may persist when transfer of the material from guinea pig to guinea pig is made. Indeed, the virulence may even retrograde under such conditions. Rather difficult of satisfactory explanation is the fact that the acid-fast bacilli passing through Cooper and Petroff's filters failed to infect animals, even though derived from a virulent culture. It is possible that the age of the filtered cultures diminished their virulence to this extent.

These several considerations harmonize well with the conception that in filtrates we are dealing with something physiologically different from the "normal" tubercle bacillus. They are not so readily explicable on the hypothesis that a very few bacilli may have slipped by the pores of the filter. The mere fact that some of the filter pores are sufficiently large to permit bacilli to pass should not be allowed to confuse our perspective of an array of considerations of which the above are examples.

We would also remind the cavillers on filtration technique that in cultures of bacteria other than tubercle bacilli we have shown clearly that, when gonidia were demonstrable, filtration results were positive, but negative when the identical bacillus was not "shedding" these granules (1919, 1926). In both instances the bacillus was present, and the filter pores were big enough to let it through, yet only the cultures with granules passed.

But apparently it has remained for Dr. Philip B. Hadley[5] to extend this

[5] Personal communication.

point of view with the most convincing evidence that has yet come to our attention. Indeed, it would seem to answer categorically those who are still unable to rouse themselves from the dominance of the pleomorphic anachronisms respecting the biology of bacteria.

In a study to be published soon he has what he believes is conclusive evidence that the filterability of many microörganisms at least is a function of gonidial reproduction. Starting with the nonfilterable, highly toxic and virulent form of *B. Shiga* (S or R type), for example, by a standardized cultural technique he dissociates the strain into one producing numerous gonidia,—his G-type culture.

This G-type is stabilized as such, and can be passed through V, N, or W filters at will, even by gravity filtration. The antecedent S-type, from which it is derived, is not filterable; nor is the R-type. But of paramount importance is the fact that the G-filtrates are cultivable at will, first as very delicate and almost invisible coccus-like elements which eventually revert to the original S-type culture. A standardized technique following lines first established by Hauduroy (1927) is also responsible for the germination of the filterable elements.

Of importance too is the fact that Hadley's G-types either are totally lacking in virulence and toxicity or are of diminished virulence. This, as well as the other high lights of his study, confirms the major premises of this paper as well as our own previous studies which have helped to build the newer biology of bacteria.

To attempt to explain satisfactorily these new considerations in the light of old and outworn traditions is attempting to "pour new wine into old bottles;" which may explain, too, an enormous number of observations of the French school, with so few of them conclusive. It should be restated then, that, if there is a filterable phase of the tubercle bacillus, its significance lies in a probable changed biophysiology often incident to evolutionary life-history stages. The filter should be looked upon as a convenient isolation method for a phase of the microörganism possibly important in pathology, and not as a source of physicochemical quibbling in a manner so detached as to disregard all other important aspects of the situation.

The question of spontaneous tuberculosis is also to be considered. If this condition is as common as Perla (1927) would have us believe, it would indeed become a question of much more significance in such experiments as this than would ordinary filtration technique. We can only say that, as far as our own experience goes in over fifteen years of autopsy-

ing animals that have died from one cause or another, we have yet to encounter one instance of what appeared to be spontaneous tuberculosis. We have it also from Dr. S. A. Petroff of Saranac Lake that his experience is essentially the same. Moreover, his opportunities for observation in this direction would be infinitely greater than our own. Nevertheless, all our later experiments have been conducted with this possibility in mind and guarded against in every way known to us.

If it can be definitely established that some well-recognized phase of classical tuberculosis can be reproduced through some filterable phase in the life history of this microörganism, it then becomes distinctly possible to correlate the so called atypical tuberculosis with such biological changes in the microörganism itself.

It is quite conceivable that the cachexia, which Arloing and Dufort and others encountered in many of their experimental animals, is really the result of the activities of this special phase of the tubercle bacillus. At the present time, however, we fear that we shall need more definite proof that this is actually the case, especially since their chief criterion for the actual existence of tuberculosis is the presence of acid-fast bacilli in the lymph nodes of these animals. Assuming as valid the position taken by Petroff, namely, that acid-fast microörganisms are present in some 33 per cent of normal guinea pigs, this finding, standing alone, would be of really little significance.

We have referred already to the early reports of Vaudremer and the more recent one of Sweany. Their pertinence in this connection is indicated by their claims for the germination of granules into mycelioid and diphtheroid phases of the tubercle bacillus. These phases are apt to be variable in respect of acid-fast features as well as of virulence. They either require repeated passage through animals for restoration of typical pathogenic characters, or they produce lesions that are not recognizable as tuberculosis.

In light of the well-known fact that the lipoidal fraction of the microorganism is chiefly responsible for the characteristic histopathology of the tubercle, the above claims are of decided interest. Based on our experience with other microörganisms it is quite conceivable that microorganisms passing through stages of this sort may develop new types of the group itself, yielding under these more or less special conditions very atypical reactions in animals. On this hypothesis the way would then

be open to explain many atypical tuberculoid changes that occur in the human species and in animals.

SUMMARY

1. Employing filtrates from tuberculous material from sixteen different sources, two animals out of a total of 37 have yielded definitely positive findings. Classical tuberculosis has been reproduced and the typical Koch bacillus recovered in pure culture.

2. These positive results have come only when the original material was richly seeded with the granular form of the tubercle bacillus. But not all animals inoculated succumbed.

3. From the same granular sources two other guinea pigs have also developed lesions which are possibly tuberculous, but which were not significant enough in the gross to warrant further injection or culture. Evidence for the correctness of the filtration point of view can, in the beginning at least, be based only on definitely positive results.

4. In the absence of an isolatable tubercle bacillus from lesions which are histologically indistinguishable from known tuberculosis, we are not, with our present knowledge of the life history of the tubercle bacillus, justified in drawing conclusions as to filterability.

5. On the other hand, histological evidence of tubercle in guinea pigs is not of itself sufficient proof of filterability. Such lesions have in our experience been caused by gram-negative paratyphoid-like microörganisms. This was shown, not only by the isolation and pathogenicity of the latter, but also by the failure of the histological *tubercle* to produce true tuberculosis when reinjected. The relation of this group of microorganisms to lesions indistinguishable from the necrobiotic type of tubercle lesions in pigs must always be kept in mind.

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A STUDY OF PULMONARY TUBERCULOSIS IN CHILDREN[1]

A. LEVINSON

A study of 119 cases of tuberculosis in children, of which 25 were white, 11 Mexican and 83 negro, treated at the Cook County Hospital (1), impressed us with the fact that pulmonary involvement is frequent in active tuberculosis of childhood, especially in negro children. Not only did pulmonary tuberculosis manifest itself in the acute forms, such as the miliary type and acute tuberculous pneumonia, but also in the subacute and chronic forms. We consider these facts especially interesting because of the still unsettled controversy as to the frequency of pulmonary tuberculosis in children, especially in the chronic form; also because of the additional question whether chronic pulmonary involvement in tuberculous children, when it does occur, is of the fibrous type of tuberculosis, or of the caseous type. In some of our cases the question arose of whether the pulmonary symptoms were due to compression of lung tissue by tracheobronchial lymph nodes, or to actual involvement of the pulmonary tissue. The existence of epituberculosis also had to be considered.

ANALYSIS OF CASES

Our cases may be divided into three groups as far as pulmonary involvement is concerned: (1) generalized miliary tuberculosis, (2) acute tuberculous pneumonia, and (3) subacute, or chronic pulmonary involvement.

Miliary Tuberculosis

Miliary tuberculosis still constitutes the bulk of acute pulmonary involvement in children. Although miliary tuberculosis involves practically every organ in the body, studding it with miliary tubercles, it is the lungs that suffer the brunt of infection. Next to the meninges, which are frequently involved in the last stages of miliary tuberculosis, the lungs are the organs that produce most of the symptoms of the disease.

[1] Read at a meeting of the Chicago Tuberculosis Society, March 8, 1928.

In our series there were 69 cases of miliary tuberculosis. It should be kept in mind that many cases of miliary tuberculosis begin as an acute or chronic pulmonary disease, the miliary process developing only two or three weeks before death. A pathological study of tuberculosis in children will therefore not give us a clear picture of the frequency of pulmonary involvement without a miliary process, as the necropsy practically always shows a miliary tuberculosis.

The leucocyte count in our cases of miliary tuberculosis usually varied from 10,000 to 16,000, and the polymorphonuclear forms varied between 65 and 70 per cent. Occasionally a leucopoenia was present before secondary infection occurred.

It may be interesting to note that all our cases of miliary tuberculosis gave negative tuberculin tests. In some instances the tuberculin tests, which were positive when the patient entered the hospital,

TABLE 1

Incidence and type of pulmonary involvement in 119 cases of tuberculosis in children

TYPE	NUMBER
Miliary	69
Acute pulmonary	15
Subacute or chronic pulmonary	15
	99

became negative later when the generalized miliary process developed. This is at variance with the experience of Hempelmann (2), all of whose cases reacted positively to tuberculin.

The following case may illustrate the change in tuberculin reaction when the miliary process sets in:

Case 1: H. W., 10 years of age, colored male, was admitted to the Cook County Hospital September 12, 1927, with a history of cough and loss of weight for three weeks. The patient had pneumonia five months earlier, from which he recovered. The child had a septic temperature and had dulness over the entire right side of the chest, anteriorly and posteriorly. There were scattered dry râles over the right chest, and bronchial breathing over the right upper lobe. The Pirquet test was positive. A diagnosis of tuberculous pneumonia was made, although an acute pneumococcus pneumonia of the right lung superimposed on a hilum tuberculosis was considered. The patient lost weight, continued to have the septic temperature, and became drowsy. The Pirquet and Mantoux tests became and remained negative, and the

patient developed tuberculous meningitis. The cerebrospinal fluid removed September 30 was clear; the pressure measured 11 mm. of mercury; there were 88 cells per cmm., all of which were lymphocytes. The Pandy test was positive, and the cerebrospinal-fluid sugar was 25 mgm. per 100 cc. The patient died on October 15, 1927, and the necropsy showed miliary tuberculosis in all the organs of the body, and a caseous tuberculous process of the right lung.

Acute Tuberculous Pneumonia

It is often hard to differentiate between the pneumonic form of miliary tuberculosis and acute tuberculous pneumonia. At best the diagnosis is not clear-cut. Even the postmortem examination may not be of great assistance. As pointed out above, many cases of acute tuberculous pneumonia terminate in a generalized miliary process; however, the consolidation of one or more lobes of the lung, persistent cough, rapid wasting, and X-ray findings of consolidation with or without small cavities, and without symptoms of generalized miliary tuberculosis such as tuberculous meningitis, speak for acute tuberculous pneumonia.

As far as was possible to ascertain, 15 cases in our series suffered from acute tuberculous pneumonia. In most of these the X-ray showed some cavitation.

One of the most interesting things was the frequency of extensive involvement of the lung. One case showed an extensive pulmonary involvement with many cavities over the entire lungs. Another had an involvement of the whole right side. A number of cases showed involvement of more than one lobe.

There was usually a moderate leucocytosis in acute tuberculous pneumonia.

Chronic Pulmonary Tuberculosis

Until recently chronic pulmonary tuberculosis was considered very rare in children. Fishberg (3) states as follows:

> We also know that tuberculosis in children is anatomically and also clinically not of the same character as that in adults. In the former the glands, bones and joints, while in the latter the lungs, are mainly the organs which bear the brunt of the infection. Indeed considerable harm is done to children by treating them for chronic pulmonary tuberculosis when before the eighth year of life they practically never have it.

Holt and Howland (4) believe that chronic tuberculous bronchopneumonia does occur in children. To quote:

> In children who have passed the seventh or eighth year the pathological process resembles that in adults; but in younger children, and especially in infants, nothing corresponding to it is met with.
> At this period the nearest approach to this condition is seen in the case of tuberculous bronchopneumonia, which runs a slow, irregular, and somewhat chronic course. The essential feature of the process in these patients is a chronic interstitial bronchopneumonia with tuberculous nodules which rarely undergo softening, but usually become capsulated.

In 1920 Eliasberg and Neuland (5) described a chronic involvement of the lung, which they named *epituberculosis*, and which has since attracted a great deal of attention. These authors saw infants and children who were infected with tuberculosis, and who had dulness and bronchial breathing over a portion of the lung, especially over the right upper lobe, without or with very few râles. X-ray showed intensive cloudiness of the infected lobe, but the sputum was negative for tubercle bacilli. The course of the disease was chronic, but the prognosis was good. The fever disappeared and the infiltration also disappeared after weeks and months. Even during the time of resolution there were very few or no râles. After the disappearance of the infiltration the roentgenographic picture was entirely negative, only an occasional small peritracheal and peribronchial lymph node remaining. The authors considered this infiltration a nonspecific process, superimposed on a tuberculous process, which they differentiate from the gelatinous infiltration of tuberculous origin.

In our series of 119 cases of active tuberculosis in children, we encountered 15 cases of pulmonary tuberculosis which ran a subacute or chronic course. Some of our cases improved for a while and made us think of epituberculosis. However, the subsequent course of the disease convinced us that, with the possible exception of one case, our patients suffered from active pulmonary tuberculosis.

Those cases which came to autopsy revealed the presence of caseation and ulceration extending over all or part of one or both lungs. In those that did not come to necropsy the clinical findings spoke for extensive pulmonary involvement of a tuberculous instead of an epituberculous nature. The following cases are taken as typical examples:

Case 2: J. O. The patient was a Mexican male, three years old, and was brought to the Cook County Hospital by the Health Department, with the following complaints: cough, peevishness, fatigue, rise in temperature, pain in the right knee and night-sweats. The mother had died of tuberculosis at the age of 19 years, about nine months before this child's admission, and a younger child had died of tuberculosis two months before. Physical examination on admission revealed dulness over the right upper and middle lobes, and diminished resonance over the left upper lobe. Bronchial breathing was present over the entire right upper and middle lobes. There was whispered bronchophony to the fourth dorsal vertebra. The Pirquet test was strongly positive, and the sputum was also positive for tubercle bacilli. The white blood count was 22,000. The X-ray showed a small amount of fluid on the left side and mottled density in the lower outer portion of the right upper lobe. The diagnosis at this time was pulmonary tuberculosis of the right upper and middle lobes. The patient remained in the hospital seven and a half months. The temperature during this time ranged between 98° and 100°F., with an occasional rise above 100°. The physical findings were limited for a number of months to the right upper and middle lobes. With the advance of time the X-ray showed cavities of the right upper lobe. The white blood count went down, so that on November 11, 1927, the white blood count was 14,250, with 50 per cent polymorphonuclears and 47 per cent lymphocytes, and on December 15, 1927, the white blood count was 8,200, with 60 per cent polymorphonuclears and 40 per cent lymphocytes. As the disease advanced there were signs of involvement also in the left lower lobe (figure 1). The patient became constantly weaker and died on January 16, 1928. Necropsy revealed an extensive caseoulcerative process all over both lungs, especially over the right upper and middle lobes.

Comment: This case was one of pulmonary tuberculosis, which ran a chronic course of seven and a half months' duration, but which was constantly progressing, starting with an involvement of the right upper lobe and spreading to the rest of the lungs.

Case 3: H. J. The patient, a colored male, three years old, was brought into the Cook County Hospital by the Health Department on May 23, 1927. No history was obtained. The physical examination on admission revealed a pleural friction rub on the right side, a right facial paralysis involving the eyelid and mouth, a matted cervical adenitis on the right side, paravertebral dulness, and a positive neck-Brudzinski. On June 6, a spinal puncture was done and the cerebrospinal fluid was negative except for a slight increase in pressure. Blood Wassermann test was negative. The Pirquet test was strongly positive. The Mantoux was also positive. An X-ray taken on June 7 showed a hilum infiltration. On June 16, 1927, the diagnosis was

bilateral tuberculous adenitis, hilum infiltration, and complete right facial paralysis. A spinal puncture done June 17 yielded a clear fluid under increased pressure, with a high cell count. On July 21 there was dulness in the left chest posteriorly, and bronchial breathing over the right upper lobe posteriorly. An X-ray taken two weeks later showed involvement of the left upper lobe (figure 2). One week later there was dulness over both upper

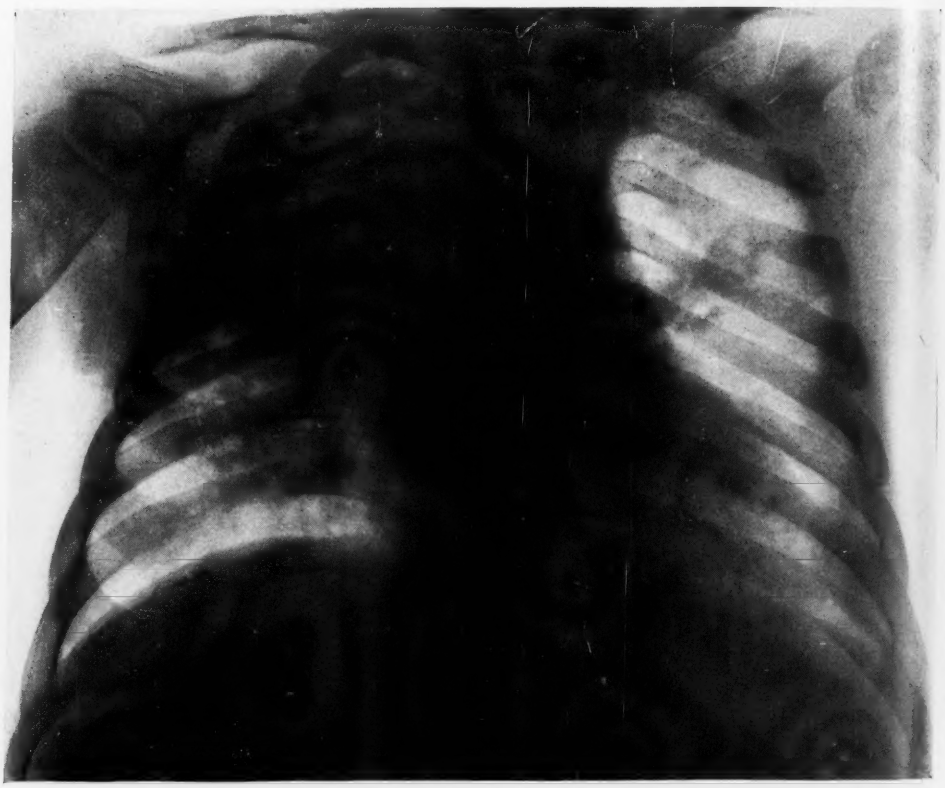

FIG. 1. J. O. X-ray of chest, 6½ months after entrance to hospital, showing extensive involvement of right upper and middle lobes, and less marked involvement of left lower lobe.

lobes, especially over the left, bronchial breathing over these areas, and occasional dry râles over the right lower lobe posteriorly. On October 31, dulness and bronchial breathing were found over the right lower chest. There was also tenderness of the neck. The impression at that time was that the child was suffering from a chronic pulmonary tuberculosis, cervical adenitis, and early Pott's disease of the cervical spine. An X-ray, however, taken at that time showed the spine to be uninvolved. Up to this time the child coughed

very little and seemed comfortable, at times running an afebrile course. About the latter part of November the patient began to go down hill, refusing food, coughing more than formerly, and having a low-grade temperature. On December 2 a spinal puncture was done. The fluid was under increased pressure, gave a positive Pandy, and contained 60 cells per cmm. Three days later the patient became stuporous and coughed severely, but had no

FIG. 2. H. J. Enlarged hilum, and shadows in left upper lobe

meningeal symptoms. On December 7, there was nystagmus and strabismus, marked emaciation, numerous râles all over the chest, and the patient was comatose. He died on December 8. Permission for a postmortem examination could not be obtained.

Comment: At first the massive involvement of the lung with the marked tracheobroncheal adenopathy suggested the possibility of epituberculosis. The subsequent clinical course and the fatal outcome proved the case to be one of chronic pulmonary tuberculosis.

Case 4: F. M. The patient, a white male, six years old, was brought to the Cook County Hospital with the following complaints: foul breath for two years, loss of 15 pounds in two years, irritability and night-sweats six months, cough two months, diarrhoea and epigastric distress one week. The family history was negative. Physical examination on admission revealed dulness and bronchial breathing over the right supraclavicular and infraclavicular regions, dulness over the right apex and upper one-third of the right scapula, and occasional râles, but no bronchial breathing; positive D'Espine, hypertrophic tonsils and cervical adenopathy. There was an ulcer on the posterior wall of the pharynx. An X-ray showed involvement of the right upper lobe. The left lung showed hilum markings. The Pirquet test was negative on entrance. The diagnosis at that time was (1) chronic pulmonary tuberculosis of right upper lobe, (2) hypertrophic tonsils and cervical adenopathy, and (3) ulceration of pharynx. The patient was discharged on September 20, 1927, and was readmitted on November 18, 1927, with a temperature of 102.4°, cough, and hoarseness. There was dulness over the right upper lobe, anteriorly and posteriorly, with bronchial breathing over the same area. On November 26, 1927, the Pirquet and Mantoux tests were slightly positive. The child was afebrile and comfortable. There was suspicious bronchial breathing over the right upper lobe anteriorly and posteriorly. The D'Espine sign was positive to the seventh dorsal vertebra. On December 8, 1927, there was inequality of the supraclavicular space, increased muscle tension on the right side, dulness over the right supraclavicular and infraclavicular spaces, exaggerated breathing, and numerous crackling râles in the right upper lobe. The patient was afebrile. On December 18, 1927, the patient went home. On December 29, he was readmitted with oedema of the face, the left side worse than the right, and laryngitis. The lung findings were the same as on discharge and the abdomen was distended. On January 19, 1928, ulceration of the epiglottis was found. The patient died a few days later.

Comment: The clinical course impressed one as being that of a chronic pulmonary tuberculosis, with a fatal termination.

The following case is the one exception in our series, which apparently recovered in spite of an extensive pulmonary involvement.

Case 5: L. S., colored male, 29 months of age, was admitted to the Cook County Hospital on November 27, 1927, with a history of coryza, fever, cough and loss of weight of one month's duration. He had dulness over both upper lobes posteriorly, with bronchial breathing over the left apex. The sputum and Pirquet tests were negative, but the Mantoux test was positive. Diagnosis of a left upper pulmonary tuberculosis was made. The X-ray showed a consolidation of the entire left lung with an area of localized pneu-

mothorax. The leucocyte count was 28,000 with 80 per cent polymorphonuclears. The child continued to run an irregular temperature, from 99° to 102°, for four or five weeks, but after that time was improving and was very comfortable.

Comment: The last we heard of the patient he was still doing well with few if any symptoms and physical findings. This brings up the question whether the patient was suffering from pulmonary tuberculosis and recovered from it, or whether it was possibly an epituberculosis. We hope to settle the question by further physical examination and roentgenography.

DIFFERENTIAL DIAGNOSIS

No matter how good a diagnostician one may be, one often has to depend on the course of the disease or on autopsy to establish the diagnosis of pulmonary tuberculosis. We learned that the way to diagnose pulmonary tuberculosis in children is to take into consideration the history, physical findings, X-ray, and the tuberculin tests. We have paid a great deal of attention to history of contact, to color, and to previous diseases. A history of contact with a tuberculous patient stamped the patient as tuberculous in our eyes. We do not believe that race *per se* plays a great rôle in susceptibility to tuberculosis. It is more likely that the economic conditions, under which certain races such as negroes and Mexicans in this country live, make them more susceptible to tuberculosis than other races.

The X-ray is another means of diagnosis, although at times it is difficult to differentiate tuberculous from nontuberculous lesions by the X-ray. Tuberculin tests, when positive, helped us in establishing the diagnosis at least of the presence of a tuberculous infection. When the tuberculin test was positive at first and later became negative, with an exacerbation of symptoms, we considered it as pointing to a development of a miliary process.

The reason for the difficulty in diagnosis is the fact that pulmonary tuberculosis may simulate many other conditions, and *vice versa*.

Miliary tuberculosis may be simulated by grippe, nontuberculous bronchopneumonia, typhoid fever, meningitis, and other infectious diseases. At times the diagnosis is hardly possible before the snowflake appearance in the X-ray, or before the appearance of meningitis. In the meningeal stage the diagnosis of a miliary tuberculosis is made easier by the examination of the cerebrospinal fluid.

Acute pulmonary tuberculosis is often mistaken for acute pneumococ-

cus pneumonia. It is true that the temperature in acute tuberculous pneumonia is usually lower than in pneumococcus pneumonia, and that the leucocyte count is not so high, and is often accompanied by a lymphocytosis; still, not every case is clear-cut and the diagnosis may be difficult.

Chronic tuberculous pneumonia presents a great many problems in diagnosis. We frequently had to differentiate it from nontuberculous

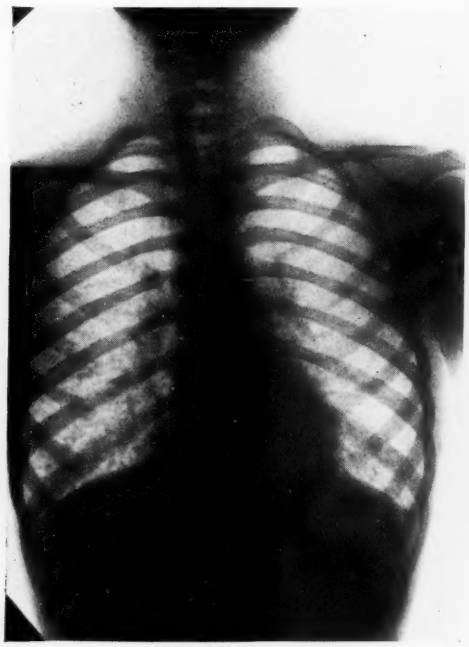

FIG. 3

FIG. 4

FIG. 3. D. M. Bronchiectasis. Originally diagnosed tuberculosis.

FIG. 4. C. J. Congenital heart disease, with marked enlargement of heart and resulting compression atelectasis of left lung.

bronchitis and from unresolved pneumonia; a number of cases that died from acute pulmonary tuberculosis were sent in with the diagnosis of unresolved pneumonia or of chronic bronchitis. Indeed it is no easy matter to differentiate these conditions.

Bronchiectasis presented some difficulty in diagnosis. The dilatation of the bronchioles can easily be mistaken for tuberculous cavities (figure 3). One case that was diagnosed as pulmonary tuberculosis proved

to be empyema. In one case the infiltration of the lungs proved to be due to a foreign body in the right bronchus. One case turned out to be an actinomycosis of the lung (6). Another case proved to be an atelectasis due to a congenital heart lesion. The case report follows:

Case 6: C. J., colored, one and one-half years old, entered the Cook County Hospital on July 27, 1927, with a history of cough and dyspnoea. The admitting-room diagnosis was miliary tuberculosis accompanied by meningitis. The essential findings on admission were those of consolidation of both upper lobes of the lung, especially the left, with scattered, moist râles throughout the chest. The heart was markedly enlarged, and there was a loud systolic murmur over the pulmonic area. Repeated Pirquet tests were negative. X-ray findings were those of an immense heart with clouding of the upper two-thirds of the left lung (figure 4). The diagnosis was changed to congenital heart disease with compression atelectasis of the left lung. The lung findings remained stationary and constant for four and one-half months, when the child developed terminal bronchopneumonia and died. The necropsy revealed a patent ductus arteriosus, and a hypertrophied and dilated heart, with atelectasis and haemorrhage of the left lung.

PROGNOSIS

The mortality in our cases was unusually high. All the cases of miliary and acute tuberculous pneumonia had a fatal termination. Of the 15 cases of pulmonary tuberculosis that ran a chronic course, 11 died, one is running a progressive course, two were lost track of, and one is doing well.

The high mortality may be explained by the fact that in a good many cases the patients were not brought into the hospital until the later stages of the disease.

TREATMENT

It is futile to speak of treatment in such advanced cases as ours. Supportive treatment is all one can give. At first we tried ultraviolet radiation when the temperature was below 101°. We found it, however, of no therapeutic value in our advanced cases.

SUMMARY

1. In a study of 119 cases of active tuberculosis, mainly in negro children, we found pulmonary involvement in 99 cases, the other 20 cases having suffered from tuberculosis in other parts of the body.

Sixty-nine were miliary, 15 acute tuberculous pneumonia, and 15 subacute or chronic pulmonary tuberculosis.

2. The tuberculin tests were negative in all cases of miliary tuberculosis. In some cases the tuberculin tests, which were positive when the patient entered the hospital, became negative when repeated after the onset of a miliary process.

3. The pulmonary involvement in both the acute and subacute forms was quite extensive and was mainly caseoulcerative in type.

4. We had to differentiate our cases from nontuberculous chronic bronchitis, unresolved pneumonia, bronchiectasis, empyema, foreign body in lungs, actinomycosis, and lung infiltration due to congenital heart disease.

5. The prognosis in all our acute cases was bad. Of the 15 chronic cases 11 died; one is living, but runs a progressive course; two were lost track of; and one is doing well.

6. We believe that the high mortality in our cases was due to the fact that the disease was far advanced when the patients came to the hospital.

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TUBERCULOUS CERVICAL ADENITIS[1]

RICHARD H. MILLER AND WILLIAM M. SHEDDEN

Tuberculous involvement of the lymph nodes of the neck, with its chronic state of infection, tumor, abscess, sinus and scar-formation, as well as its distant complications, still continues to be a source of worry and distress, not only to the surgeon but also to the general practitioner. The treatment of these lymph nodes has passed through two chief eras; until a few years ago the proper therapy was considered to be extensive neck dissection, but recently the tendency has been chiefly toward conservative palliative measures. A number of years ago one of us (1) reported from this Clinic a series of cases treated for the most part conservatively, and at that time we were impressed with what we considered the therapeutic value of tuberculin (*B. F.,—Bouillon Filtrate*), and we so recorded our conclusions. Further study, and the observation of several hundred additional cases, have led us to modify our opinions, and the object of this paper is to review briefly certain modern conceptions of tuberculous infection, to report a certain group of cases which we have elected to study, and to record certain definite impressions which we have gained.

The tubercle bacillus gains entrance to the body through the air-passages or gastrointestinal tract, or both. It penetrates the mucosa, comes to rest in the submucosa, whence, in almost all cases, it is carried by the lymph-vessels to the neighboring lymph nodes. The whole lymphatic system plays a very important rôle. Krause says there is probably never any tuberculous infection of the animal body without at some time infection and almost invariably lesion of some lymph-vessels and nodes (2). He adds that, while a large number of lymph-node infections occur as isolated processes, probably there is never, except in the very beginning, any tuberculous focus in the body without its being in a lymph node somewhere (2). Furthermore, Krause, Miller and Willis (3) regard human infection as more diffuse or "constitutional" than has commonly been accepted. They say it is a disease not unlike

[1] From the Nonpulmonary Tuberculosis Clinic of the Massachusetts General Hospital, Boston, Massachusetts.

syphilis, "of numerous loci of infection, yet with few manifest foci of anatomical changes." Clinically there is a benign general infection,—a very low grade bacteriaemia quite different from miliary tuberculosis. This idea of tuberculosis as a generalized disease is echoed by Mayo (4), who at the same time throws some weight on the scales on the side of operation:

> Many of the ablest exponents of the treatment of tuberculosis believe that if the primary tuberculous focus, where the bacilli enter the protective mechanism of the body, become acclimatized, and first involve the lymphatic system, can be removed, the secondary processes will thereby be rendered much more amenable to treatment.

In normal guinea pigs Krause and Willis (5) found that, following subcutaneous or intracutaneous inoculation of living tubercle bacilli, the bacilli were carried away by lymphatics within one hour, and made the circuit of the body within three or four days. In immune animals this spread was much retarded. The inescapeable inference, the fact which all students of the subject realize, is that soon after the establishment of the primary focus of disease there may be a spread of bacilli over the body,—frequently subclinical and without signs or symptoms. We are more and more impressed with the importance of either early control or early extirpation of these foci of infection.

In our consideration of the progress of the infection in tuberculous adenitis, the following paragraphs from Pottenger (10) are worth quoting:

> When the primary focus is caused by many bacilli, the germs not only pass quickly to the lymph nodes but they may pass beyond them before the cells become sensitized. They may rapidly make the entire circuit of the body, being detained here and there, and establishing foci in many tissues and organs. This type of infection usually causes death of the host.
>
> When primary infection is once established, before it heals completely, repeated reinfections of nearby or even distant tissues usually take place. These, as a rule, are caused by few bacilli and heal, producing an ever-increasing immunity on the part of the host. By this means a high grade of immunity is often established, which serves as a competent protection for the individual against future endogenous or exogenous infections.

In our Clinic at the Massachusetts General Hospital we are continually being struck with examples of this statement. A case of cervical

adenitis which has been improving under the best hygienic and palliative treatment will suddenly show evidence of a distant metastatic infection, such as eye tuberculosis, skin involvement on the legs, disease of the inguinal or axillary lymph nodes, or even pulmonary infection.

That tuberculous infection of the cervical lymph nodes comes, in the vast majority of cases, through the tonsils and adenoids, is so well proved that it need not be discussed. As long ago as 1918 Wood (6) proved that about 5 per cent of all tonsils showed evidence of tuberculosis. Other authors put the figure higher and lower, but 5 per cent is a fair figure. He further found even more cases of pharyngeal tonsils with tuberculosis, that is, 10 per cent (7).

The anatomy of the cervical lymph nodes merits brief comment here, to recall to attention, first, that the tonsils drain direct into the upper anterior lymph nodes of the deep cervical or carotid group, whereas the pharyngeal tonsils (adenoids) drain direct to the more posterior of the nodes of this group. Tonsillar lymph nodes first become palpable behind the angle of the jaw, anterior to the sternocleidomastoid muscle, while the lymph nodes secondary to the adenoids are first felt behind the upper end of the sternomastoid. These substernomastoid nodes empty into a lymph-vessel called the jugular trunk, which is joined by another lymph-vessel from the supraclavicular lymph nodes, and then drains into the subclavian vein on the right and the thoracic duct on the left. There is no direct lymphatic trunk from the substernomastoid lymph nodes to the supraclavicular nodes, nor is there a trunk connecting the cervical with the tracheobronchial or mediastinal lymph nodes. These facts are of clinical importance, because they argue against two attractive theories:—first, that there is direct lymphatic extension from the tonsils to the apex of the lung, and, second, that there is similar extension from the cervical to the mediastinal lymph nodes. Grabfield and van Zwaluwenberg (8) (9) have adduced interesting evidence pointing to the occurrence of tuberculous involvement of the apical pleura by direct extension *via* the cervical lymph nodes from the tonsils. This is not commonly accepted as the method of infection of the apex of the lung; the authors and Grabfield are now working further on this problem. Second, by the consideration of the anatomy of the lymphatics, as well as by clinical experience, we believe we can dispose of the idea that tuberculous infection extends directly *via* the lymphatics from the neck to the tracheobronchial lymph nodes, or *vice versa*.

The path taken by the tubercle bacillus, from its point of arrest under

the mucous membrane (Krause) is as follows: To the neighboring lymph nodes, thence by lymphatics to the venous system, to the lung, whence it may or may not go to the tracheobronchial lymph nodes. From the lung it may get into the pulmonary vein, thence to the heart, and around the body through the arteries. This results in a benign general infection. Weber (11) speaks of this bacillaemia as a cause of erythema induratum; he considers it a not infrequent condition, overcome or held in abeyance by bodily resistance. Stokes (12), discussing this subject as a manifestation of tuberculosis, mentions the case of a woman who died of tuberculous meningitis thirty days after the onset of an erythema induratum. Beckwith and Millzner (13), in a diagram of the lymphatic drainage of the pharynx and trachea, show how an infection in the tonsils may go to the superior deep cervical nodes, inferior deep cervical nodes, thoracic duct or right lymphatic duct, subclavian vein, right heart and pulmonary arteries, thence to the lung. Further examples of the bacillaemia of lymph-node tuberculosis may be found in the occasional reports in the literature of cases of generalized tuberculous adenitis, of which the authors have seen at least two. Such a case was recently reported by Criep and Narr (14) in which the diagnosis was made by the biopsy of an epitrochlear lymph node.

All the above references to the early low-grade bacillaemia, which occurs after the establishment of a focus of tuberculous infection anywhere in the body, are cited for the purpose of leading up to the statement of our belief that the same thing may be true in cervical adenitis, and that in our treatment of this condition we must bear in mind not only the proper handling of the local disease in the neck, but also we must not lose sight of the fact that the lymph nodes either may be about to set bacilli free into the circulation, or may already have done so and are going to do so again. It is one thing to treat a local infection where the worst that can befall the patient will be confined to the tissues of the neck, but quite another to treat a focus which is probably feeding the body with bacteria which are capable of doing infinite harm later. Myers (15) mentions that in childhood, the most common period for the occurrence of tuberculous cervical adenitis, the lymph nodes function better as filters than at any other age, the bacilli may live a long time in the nodes without causing any changes discoverable on examination or by X-ray, and that tuberculosis of lymph nodes heals more readily than that anywhere else in the body. These facts are admittedly true, but do not warrant our regarding the infection with complacency. In a recent

article Connerth (16) reported from a sanatorium 5,156 cases of tuberculosis, of which 391 had diseased cervical lymph nodes, and of these 391, 25 per cent developed pulmonary disease; and he remarks that tuberculous lymph nodes seem to give some immunity against pulmonary involvement before puberty, but not after. It might be said that these 25 per cent developed phthisis as a result of cervical adenitis, and that in the other 75 per cent the nodes gave immunity. Our problem is to ascertain the best method of treatment, and the best method is not to try to shut these bacilli up, because that cannot with surety and safety be done, but to kill them or remove them. The infection goes, from the tonsils or adenoids, direct to the cervical nodes, and there must be a period, after the lymphatic involvement, when the disease is confined to these lymph nodes,—a period before any bacilli break through into the circulation. If we can attack the nodes at this best of all times, we have a golden opportunity to eradicate the disease.

The treatment of tuberculous cervical adenitis first passed through an era of radical surgery, when extensive and multilating operations were ruthlessly performed, with poor results, nerve-paralysis deformities, and unsightly scars. Now, in recent years, the tendency is all toward conservative measures, with the use of general hygiene, rest, heliotherapy, artificial sunlight, X-ray, less often tuberculin, and surgery only when especially indicated. We will here briefly review the present status of some of these methods of treatment.

1: General Hygiene: This needs no comment, as its value and importance are recognized by all. Under this heading we would class the removal of the tonsils and adenoids. We believe this should be done in all cases of cervical adenitis, even though neither the tonsils or adenoids show gross evidence of disease. It may be argued that in many instances this is a case of "locking the barndoor after the horse is stolen," but if these tissues have ever fed tubercle bacilli into the neck they are probably still doing so.

2: Rest: This is an ideal form of treatment, hard to achieve, but to be recommended whenever it can be attained.

3: Tuberculin: Tuberculin, in one of its various preparations, has for years been commonly employed in diagnosis, and less frequently as a therapeutic agent. Since the founding of our Clinic we have used it consistently, and have reported what we believed to be a favorable series of results (1). Of some recent workers who have spoken in favor of tuberculin therapy are Schmidt (29), Deycke (30), Crowley (31), Macrae

(32), Elliott and Sheard (33), and Abbott (34). We have always used the *B. F.* or *Bouillon Filtrate*, from the Saranac Laboratory for the Study of Tuberculosis. While we are convinced that there are certain cases of lymphatic tuberculosis in which it does good, we have come to the conclusion that in the general run of cases it is of doubtful efficacy.

4: Light Therapy: a: Heliotherapy: Heliotherapy is well recognized as a very important factor in the treatment of tuberculosis, as well as other diseases, and it has been perhaps most actively used by Rollier, who has written very extensively on the subject. In a recent article (17) he discourses enthusiastically on this form of therapy in surgical tuberculosis, saying that it stimulates pulmonary and circulatory activity, increases the appetite, and exerts a favorable influence on digestion and the activity of the endocrine glands. In pulmonary diseases sunlight is best in convalescence, and its use is to be deprecated in the presence of an active process in the lung (Pollock (18)). The sun's rays help in the prevention and cure of rickets, aid pregnant women in maintaining a normal calcium metabolism, and their effect on patients with tuberculosis "is also associated with a rise in blood-calcium" (Pottenger (19)). We should like to quote a few lines from Bullock (20), who, in speaking of the light treatment of bone, joint, and lymphatic tuberculosis, says

> Let us recall, in the midst of all the prevalent enthusiasm for heliotherapy in bone and joint cases, that forty or more years ago Louis A. Sayre of New York taught us how to get good results in such affections; that rest was a pivotal point then, as it is now, in the treatment of all varieties of tuberculosis. Nowadays it seems quite the mode to forget some of the good work that has been done by our predecessors. Many of these lesions are due to the bovine tubercle bacillus, are slow and chronic, and are prone to recover from active symptoms if given a chance. I am sure that in my young days in medicine in New York I saw all the things occur that are now so loudly acclaimed as exclusively due to heliotherapy.

Closely allied to heliotherapy is (*b*) *Ultraviolet Therapy:* Any detailed discussion of this subject is beyond the scope of this paper. Countless articles, favoring this form of treatment may be found in modern literature. Ultraviolet light has apparently some deleterious effect on tubercle bacilli directly exposed to its rays; it may make them non-acid-fast, and irradiations from a mercury-vapor-quartz lamp are said to kill tubercle bacilli in sputum when they are exposed for five minutes at a distance of

10 inches (21). Of course, the same action cannot be claimed for the rays on bacilli in the living tissues of the human body. It is generally considered that the treatment is contraindicated in nonpigmenting persons, in the very ill, the very young and the very old, and in the presence of fever or amyloid disease. We have had rather extensive experience with these ultraviolet rays, and believe that they are effective and worth trying, especially in cases with tuberculous sinuses, fistulae and ulcers. They aid in building up the general condition of the patient, but in our experience have had no marked effect on cases with lymph nodes of any material size. We believe they are of value when indicated, but we deprecate the present widespread use of them without proper medical supervision.

5: Roentgen Ray: From the early part of this century the roentgen ray has been used in the treatment of surgical tuberculosis, many enthusiastic reports of its efficacy being found in the literature. For the most recent and complete study and bibliography of the subject the reader is referred to the excellent and comprehensive article of Hanford (22), printed in September, 1927. He says

> Small doses of filtered roentgen ray given at intervals of less than three weeks appear to shorten the course of the disease and to favor resolution or marked improvement in all stages (except cold abscesses) in a sufficiently large percentage of cases to justify the conclusion that the roentgen-ray is useful in the treatment of tuberculous glands of the neck.

Hanford notes that the cases most helped are those with tuberculous sinuses, and those with small lymph nodes; and that 40 per cent of cystic swellings resolved without incision or spontaneous opening. He found that of 141 patients 47.5 per cent were apparently cured in an average of ten months, and 23.4 per cent were "so markedly improved when last seen as to make the treatment appear satisfactory." He adds that other methods of treatment, minor and major surgical operations, should be employed when indicated.

Our experience with the roentgen ray is too limited to enable us to speak with the slightest authority. We have been using it in a number of cases, especially with scattered small discrete nodes, and as far as we have gone the results have been good rather than bad. In one case of rather extensive lymph nodes, in a young man, the last treatment was followed in a few days by the onset of virulent miliary tuberculosis, which resulted in death in a short time, but we could not prove that this

was in relation to the treatment. We advocate the use of the roentgen ray in selected cases.

5: Operation: We shall refer to surgical operation later; here it is our intention to mention briefly certain tendencies of the present-day surgeons. The trend has been all away from radical surgery, trusting rather to palliative measures and to the patient's ability to overcome his infection,—with help, of course. Some surgeons still favor radical operation when it can be done, and the good results of Ladd (23) and Dowd (24) are well known. Their work has been mostly with children, in whom the lymph nodes more readily lend themselves to clean extirpation. Hanford (25) believes in it in selected cases, and we have come to favor it more and more. Gibson (27) speaks of the "hideous results" of complete extirpation and the "horrid scars" which are a consequence of a routine of *laissez faire*. There were "hideous results" in the old days; they are rare to-day in the hands of competent surgeons. The horrid scars of conservative treatment of suppurating lymph nodes have certainly not impressed us. Scars on the neck are preferable to miliary or pulmonary tuberculosis. Gibson adds, "It is our belief that careful attention to and long application of well-recognized nonsurgical procedures should be maintained before a final decision is reached that any given case requires surgical intervention." We believe that while these nonsurgical procedures are being carried out the lymph nodes are every now and then liberating tubercle bacilli to be carried over the body. Lahey and Clute (26) in 1922 reported 48 cases operated on by various men in a large general clinic with 43.4 per cent of good results, 26 per cent of the cases with paralysis of the spinal accessory nerve, 5 cases of paralysis of the depressor anguli oris, and 8 recurrences. They rightly deplored these results, which would have been infinitely better in the hands of one man who studied the subject carefully. Then, in an excellent recent paper in 1927, Clute (28) reports 131 cases from the Lahey Clinic, with very good results, and marked decrease in nerve injury (only one case). He mentions the value of operation in early cases, and says, "For the average patient, who cannot afford the time or expense of prolonged hygienic treatment, surgery seems the method of choice." With this we heartily agree, though we would add the factor which now influences us most strongly in favor of operation is our appreciation of the danger of these latent foci of infection.

We have had no experience with the aspiration and injection method of treatment (Calot) of the lymph nodes, admirably discussed by Gibson (27).

For the purpose of checking up an unselected group of cases of tuberculous cervical adenitis, we picked every case that was listed in the records of the Massachusetts General Hospital as having any operative procedure from 1918 to 1927. The operations included everything,—biopsy, incision and drainage, curettage, and excision. After the records had been gone over and studied, an attempt was made to follow them up, and the results show a few striking facts which merit some discussion.

Summary of the cases

Total cases	204	Left side alone	49
Males	92	Both sides	46
Females	112	Side not given	13
Right side alone	96		

There is nothing worthy of particular comment here, except that in 46, or 22 per cent, the lymph nodes were bilateral.

Ages

Under 10	17	30–39	33	60–69	2
10–19	61	40–49	11	70–79	3
20–29	73	50–59	3	Over 80	1

Average age 24.2

Our Clinic is not primarily for children, and it is interesting to note the greatest occurrence of cases between 20 and 30; further than that, there were 6 cases over 60 years of age.

Twenty-five, or 12 per cent, had pulmonary tuberculosis at the same time. This does not argue for the preventive action of cervical lymph nodes against pulmonary disease.

Forty-one cases had lymph nodes elsewhere, diagnosed tuberculous, as follows:

Axillary	23	Epitrochlear	3
Inguinal	14	Popliteal	1

This adduces further evidence in support of the generalized character of the disease.

Of these 204 cases, only 132 could be traced. Our patients are mostly of a poorer class, many of them foreigners, and most of them frequent movers; they cannot be followed up as can patients of a higher social status. This difficulty in securing final data is in spite of the fact that every case was turned over to the Social Service Department, and so far as possible their homes were visited and their living supervised.

Seventy-one returned for examination, 32 answered by letter, and 29 were ascertained to be dead. This astonishing fact, that 29 cases had died, will be studied in detail later.

The 71 who returned were carefully examined, and in estimating the results they were classed as follows:

A: Complete cure. Patient perfectly well. No further lymph nodes, or other disease.
B: The patient well, but showing one or more small lymph nodes, too small to require treatment.
C: More lymph nodes, active and requiring treatment.
D: Patient no better or worse.

The cases will now be considered briefly in groups according to the location of the lymph nodes.

I: Axillary lymph nodes: 3 cases.
A: 2 cases: complete cure.
C: 1 case. No further axillary lymph nodes, but 2 small nodes in neck.

II: Supraclavicular lymph nodes alone: 1 case. Result: A: complete cure.

III: Submaxillary lymph nodes alone: 8 cases.
A: 4 cases: complete cure.
B: 3 cases: two had small innocuous nodes; one had complete cure, but paralysis of depressor anguli oris.
C: 1 case: this patient had two small remaining nodes, not a recurrence, from failure to remove them; also slight paralysis of the depressor anguli oris.

IV: Carotid or substernomastoid lymph nodes: 59 cases.
A: 29 cases. These were all perfectly well, with no evidence of further nodes, or other tuberculosis. Of these, 21 had had excision, and 8 incision and drainage. In 6 there was mention of scars which could be improved. We consider this no contraindication to operation, because in practically every instance the appearance can be improved by a simple cosmetic operation under local anaesthesia.
B: 19 cases. All these were clinically well. Twelve had very small palpable nodes, in no case considered active, or requiring treatment. In most cases we considered them scarred or calcified nodes, but classed them under this heading. Four had scars which were rather unsightly, and two of these latter were classed *B* for this reason alone; they had no further lymph nodes.

C: 10 cases. All of these had recurrent nodes, and one had an unsightly scar. In no case were the nodes very bad. One case had had in all six operations,—a very intractable infection, which no one operation could eradicate.

D: 1 case. This was a young man of 19 who had only incision and drainage. He did not keep in touch with the Clinic, and was distinctly worse when seen.

Summing up these cases of carotid nodes, 49 per cent we classed as cured without further disease, 32 per cent clinically cured but with small palpable inactive nodes still to be found, 16 per cent with presumably active recurrent nodes, and 1 case, or 1.6 per cent, worse.

Of the total 71 who reported, 2 cases, or 2.8 per cent, had nerve involvement, and each of these was a paralysis of the depressor anguli oris from cutting the lowest branch of the facial nerve in dissecting out submaxillary nodes.

We feel that the figure of 81 per cent clinically cured is satisfactory in spite of the fact that in some of these small nodes were palpable (32 per cent). These cases were not selected, but were taken from the records as we found them. They were almost all operated on by the authors or under their direction. However, it must not be forgotten, that these are figures for the patients who reported in person. Some of the others, to whom reference will be made, are dead.

RESULTS OF LETTERS

Thirty-two patients who failed to report personally answered by letter. So far as we could classify them the results were:

A: 18 cases perfectly well.

B: 5 cases. Said they were perfectly well, but admitted to having small lymph nodes which did not bother them.

C: 1 case. No better. This operation was merely a biopsy.

D: 3 cases. No better or worse. These merit some comment, and will be discussed in brief.

1: The operation was not radical. There are now many and larger nodes.

2: The patient now has tuberculosis of the spine.

3: The patient is apparently dying of pulmonary tuberculosis.

E: 5 cases. We could not classify these.

Summing up these letter cases, 32 in number, we have 56 per cent cured and 15 per cent clinically well, although with small nodes which are not a source of symptoms, a total of 71 per cent satisfactory results.

Taking all the cases which we traced and which were living, the total of classes A and B, which we consider as satisfactory results, is 78 per cent.

The shocking thing about these cases was to find that, of the 204 whom we elected to follow up, we traced 132, and found that 29, or 22 per cent of the 132 were dead and 16, or 12 per cent, had died of tuberculosis. This means that at least 8 per cent of the total 204 are dead of tuberculosis. In assigning the cause of death we were obliged in most cases to depend on the statements of friends and others, but we believe them to be substantially correct. They are as follows:

Pulmonary tuberculosis	13	Heart disease	2
Probable pulmonary tuberculosis	2	"Status lymphaticus" (died on operating table)	1
Miliary tuberculosis	1	Cancer	1
Tuberculous meningitis	1	Arteriosclerosis	1
Tuberculous peritonitis	1	Unknown	3
Pneumonia	3		

Of the 16 cases that died of undoubted tuberculosis, the average age was 25.8 years. The youngest was 10 and the oldest 53. Furthermore, 9 had no evidence of pulmonary or other tuberculosis on entrance, 3 had definite pulmonary disease, three were doubtful, and one had an old tuberculous spine. The cases with pulmonary disease at entrance did not have any radical operation.

We believe it will be of interest to give here in very brief detail the facts of the 16 patients who died of tuberculosis.

1: Female, age 21, entered March, 1924. Very extensive nodes both sides of neck. There was no evidence of pulmonary disease and X-ray was negative. A partially broken-down area in the neck was incised and curetted. *May, 1924:* Readmitted for incision and drainage of abscess. Lungs still clear. *May, 1925:* Râles heard in chest for first time. X-ray still negative. *June, 1925:* Increase in chest signs. Readmitted some months later. There was definite tuberculosis of both lungs, with tuberculosis of axillary and inguinal lymph nodes. Died shortly afterward.

Comment: This girl had had cervical nodes for 12 months at the time of her first entry, and there was doubtless a bacteriaemia at this time, but it was not clinically evident. She had excellent hygiene and care, but the disease progressed rapidly. We believe that very early excision might have prevented this unfortunate outcome.

2: Man, age 37. Admitted January, 1924. History of nodes in right neck for six months. They broke down 3 months after onset. Had strongly positive Wassermann. Two weeks before entrance nodes in left groin began to swell. X-ray of chest suggested bilateral pulmonary tuberculosis. Biopsy was performed. Died one year after this of pulmonary tuberculosis.
Comment: This is apparently another case of early bacteriaemia.

3: Girl, age 15. Admitted May, 1919. Nodes on both sides of neck, first noticed 7 years previously. Examination of chest negative and X-ray did not suggest tuberculosis, though there was an area which had some resemblance to a lung abscess. Operation consisted only of biopsy. Patient did not keep in touch with the Clinic, but was reported to have died of pulmonary and laryngeal tuberculosis in August, 1926.
Comment: This is a case in which the cervical lymph nodes probably were the initial focus, and preceded the pulmonary involvement.

4: Girl, age 21. Admitted April, 1918. The nodes had first appeared 4 months previously, and she had pulmonary tuberculosis at entrance. Died of phthisis later the same year.
Comment: Almost simultaneous occurrence of cervical and pulmonary disease; it is impossible in this case to say which one came first.

5: Woman, age 24. Admitted May, 1917. Onset of nodes in right neck 2 years previously. Examination showed a large group of movable matted nodes; these were removed by radical operation. Patient died April 13, 1921, of pulmonary tuberculosis.
Comment: A case of infected nodes existing for two years before admission to hospital, with development of phthisis later, after removal. We believe the pulmonary involvement must have occurred before operation.

6: Man, colored, age 44. Admitted May, 1916. Nodes appeared in right neck 6 months before entrance. Diagnosis proved by biopsy, and later there was an operation for incision and drainage. The lungs were clear. Died January 14, 1921, of pulmonary tuberculosis.
Comment: A colored man, in whom bacteriaemia probably set in early after the appearance of the nodes in the neck.

7: Man, age 31. Admitted October, 1916. This patient contracted pulmonary tuberculosis 18 months before entrance, and cervical nodes 15 months later. The only operation was incision and drainage. He died of phthisis shortly after discharge from the hospital.
Comment: This was a case of advanced pulmonary disease, complicated in the later stages by cervical adenitis.

8: Girl, age 19. Admitted November, 1921. Had nodes on both sides of neck, of two months' duration. The lungs at this time were entirely negative. The nodes were large, and had grown rapidly. Incision and drainage were performed on each side. The patient died of pulmonary tuberculosis in 1926, 4½ years after onset.
Comment: This represents another case in which the cervical adenitis undoubtedly preceded the pulmonary involvement.

9: Girl, age 10. Admitted May, 1922. At this time she had tuberculous cervical adenitis, secondary to an old tuberculous spine. The lungs showed no definite evidence of disease, though it was suspected. The only operation was incision and drainage. She died 7 months after admission, of tuberculosis of spine and lungs, and chronic nephritis.

10: Girl, age 24. Admitted September, 1918. Had had small nodes in neck since childhood, but they had not bothered her until two years before entrance, when they began to increase in size. Careful supervision and hygiene had no beneficial effect. The nodes were bilateral, numerous and movable. The lungs were negative. Bilateral radical excison was performed, but some lymph nodes were left in. Then in 1919 a further excision was done, following which her general health improved. In spite of this she died two years later of pulmonary tuberculosis.
Comment: This patient was probably "tuberculous" from an early age, and the cervical nodes were doubtless but one manifestation of a more general process. In a case of this sort, of course, radical surgical removal is admittedly of no avail, except as it may do away with a painful or unsightly focus of disease and a breeding place for tubercle bacilli.

11: Man, age 34. Admitted September, 1920. A history of fistula-in-ano for 5 years, and nodes of the neck for 2 years. These nodes were bilateral. At entrance there was clinically a tuberculous process at the right apex. The only operation was incision and drainage. The patient died 3 years later of pulmonary tuberculosis.
Comment: Another case in which the cervical nodes were probably secondary to a tuberculous process elsewhere.

12: Boy, age 17. Admitted July, 1916. Had had nodes in neck for 12 years, requiring occasional incision and drainage. At entrance had nodes on both sides of neck and in groins. The lungs showed no definite tuberculosis, but there were suggestive signs. Operation consisted of incision and drainage and partial excision. The patient died of tuberculous meningitis and pulmonary disease six months after entrance.

13: Boy, age 15. Admitted December, 1918. Had had one node for two years, gradually increasing in size, and on entrance presented a hard discrete mass in the right supraclavicular triangle the size of an orange. This was completely excised. Examination of the lungs was suggestive of tuberculosis, and X-ray showed calcified hilum nodes with a suspicious sign in the right apex. The patient died of tuberculous peritonitis one year after entrance.
Comment: We think the result might have been different if radical excision had been performed when the lymph nodes first appeared.

14: Man, age 32. Admitted September, 1923. There was a history of tuberculous epididymitis 5 years before entry. Had had very extensive nodes on both sides of the neck for several months. Diagnosis proved by biopsy; no other operative procedure. X-ray showed some mottled dulness at both apices, and mediastinal nodes, but no more positive evidence of pulmonary tuberculosis. After failure to improve under careful hygienic treatment, patient was given a course of X-ray treatments. Shortly after the cessation of these treatments the nodes melted away in a phenomenal manner, but, *pari passu,* the patient became very sick, running a high temperature, and died November 11, 1924, of miliary tuberculosis.
Comment: It cannot be stated that the X-ray treatment had any actual influence in starting the final miliary process. Early removal of the nodes might have been of better therapeutic value, but they were so large, numerous and extensive, that we doubted our ability to get them all out.

15: Woman, age 53. Admitted June, 1921. This case is obscure, and is included in spite of some doubts about it. The patient was admitted with high fever, which careful examinations failed to diagnose satisfactorily, though the probable condition was thought to be milary tuberculosis. In the left neck there were nodes which had been incised and partly removed outside, 4 weeks previously. After a short stay in the hospital the patient was taken out against advice, delirious and unconscious. She died in a few days; diagnosis, tuberculous meningitis.

16: Girl, age 16. Admitted July, 1921. A very pretty girl with extensive nodes on both sides, which had begun 4 years before entrance. At entrance the lungs were clear both on physical examination and by X-ray. In spite of the most carefully supervised hygienic treatment in the country she failed to improve. Two radical operations were then performed on the neck, and one for removal of a large mass of tuberculous nodes which developed in the right axilla. In spite of every effort to save this patient, she gradually failed and died of pulmonary and generalized tuberculosis.
Comment: At entrance the nodes were so numerous and extensive that radical

operation seemed a procedure of doubtful wisdom; we wish, in retrospect, that it had been done. We believe that if the nodes had been removed when the disease first appeared the patient might be alive to-day.

SUMMARY

Tuberculous lymph nodes of the neck constitute a focus of disease which, early in its existence, may set free tubercle bacilli that are carried about the body, resulting in a mild bacteriaemia. The bacilli may come to rest anywhere in the body, and may give rise to later secondary loci of disease. The bacilli may also extend from the originally infected nodes and invade the contiguous ones, finally involving most of those on one or both sides of the neck. Anything which builds up and improves the patient's general condition, such as rest, hygiene and heliotherapy, increases his power to combat the original infection and also to overcome its possible secondary manifestations. Ultraviolet light is a valuable factor in building up local resistance, and is particularly valuable in its good effect in the healing of sinuses; it does not seem to have much influence on lymph nodes of any considerable size. The roentgen ray is, as Hanford has shown, very valuable and must be accepted as an important method of treatment. Tuberculin is of doubtful effectiveness, but seems to help some cases.

It seems to us that any form of treatment which is directed against the swollen lymph nodes, and fails to take into consideration the fact that the nodes contain living tubercle bacilli, which have been, may at the present time be, and probably will in the future be set free into the general circulation, is losing sight of the most important fact of the whole condition. In addition to the cases reported in this paper, we have seen and followed many hundreds of cases of tuberculous cervical adenitis, and we are impressed with the number of those which present distant lesions in the body, to say nothing of the deaths, secondary to lymph nodes in the neck.

We therefore wish to go on record as believing that in a considerable number of cases of early tuberculous cervical adenitis, whether in children or adults, and often in cases of longer duration in which operation is technically feasible, radical surgical operation is the method of choice. We do not fear the possibility of scars; because in the hands of a good surgeon they are not as bad as they used to be, they can be improved by simple cosmetic operations, and we prefer a scar in the neck to later tuber-

culosis of the eye or the lungs. The operation must be supplemented with all the supportive and palliative measures which may be used.

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MILIARY TUBERCULOSIS OF THE LUNGS WITH RECOVERY

A Report of Two Cases[1]

F. W. MARLOW, JR.

The purpose of this communication is to present two cases of miliary tuberculosis, diagnosed by symptoms, physical examination, and characteristic X-ray findings in the lungs, and the demonstration of a tuberculous pathological process elsewhere in the body, the respective patients both living twenty-four and fourteen months after the process was demonstrated in the lungs by X-ray.

The terms "chronic" or "arrested," when applied to generalized tuberculosis, ordinarily suggest the probability of an incorrect original diagnosis. Miliary tuberculosis commonly is understood to imply a rapidly progressing, inevitably fatal disease. But that it may, in certain rare cases, have a favorable outcome has been demonstrated with increasing frequency since the days of Waller (1), who maintained as long ago as 1845 that miliary tuberculosis was curable. A brief review of the literature reveals about 36 fairly authentic cases, although the difficulty of determination from a written story is made doubly great by the inclusion of many cases in which the isolated lesions obviously did not arise from a uniform seeding of the lungs with tubercle bacilli. True miliary tuberculosis properly should include only cases in which the individual tubercles in the lung are all at the same stage of development and presumably of the same age. The following is a tabulation of the cases which I have been able to find in the literature. A number of these are probably not true miliary tuberculosis, although classed as such by the authors.

In 1860 Wunderlich (2) reported a death from an intercurrent illness in a patient who had been diagnosed as miliary tuberculosis four months previously; autopsy confirmed the presence of the acid-fast infection. Six years later Sick (3) stated that he had found healed miliary tuberculosis in the lungs of a stone-mason. As all the lesions were of the same size, he believed that they

[1] From the Medical Clinic of the Peter Bent Brigham Hospital, Boston, Massachusetts.

were probably not inhaled particles of stone. Burkart (4) mentions instances of miliary tubercles in which the character of the tubercles furnished evidence that they had existed a considerable time before death. In addition to these, Longcope (5), in a study of 19 cases of generalized tuberculosis, reported eight which had a course sufficiently prolonged to be considered subacute or chronic. However, none of these cases lasted more than a year. Opie (6) noted a case of healed miliary tuberculosis coming to autopsy as the result of a *Streptococcus viridans* endocarditis. Von Muralt (7) reported two cases which eventually came to section as a result of meningeal involvement.

In recent years the increased frequency of X-ray examination has brought to light more and more instances of miliary tuberculosis in persons not acutely ill. One of the first of these was described by Northrup (8) in a paper presenting 8 cases of generalized infection diagnosed by roentgen examination as miliary tuberculosis. Similarly, cases have been reported by Kahn (9), Baer (10), Stivelman and Hennell (11), Blaine (12), Bierman (13), Klingenstein (14), Pierson (15), Maendl (16), Wallgren (17), and Mason and Nather (18). There are a few cases of particular interest, such as that of Preston and Jeaffreson (19), with its associated evidences of Mikulicz's disease. Middleton (20) reported a case with coincident syphilis, but gave no comment upon the effect of antisyphilitic treatment. Kahn (21) found typical radiographic evidence of miliary tuberculosis of the right lung only, and was able a year later to demonstrate tubercle bacilli in the sputum. In a paper emphasizing the value of serial X-ray examinations in these patients, Sante (22) reports a case dying after an illness of seven months.

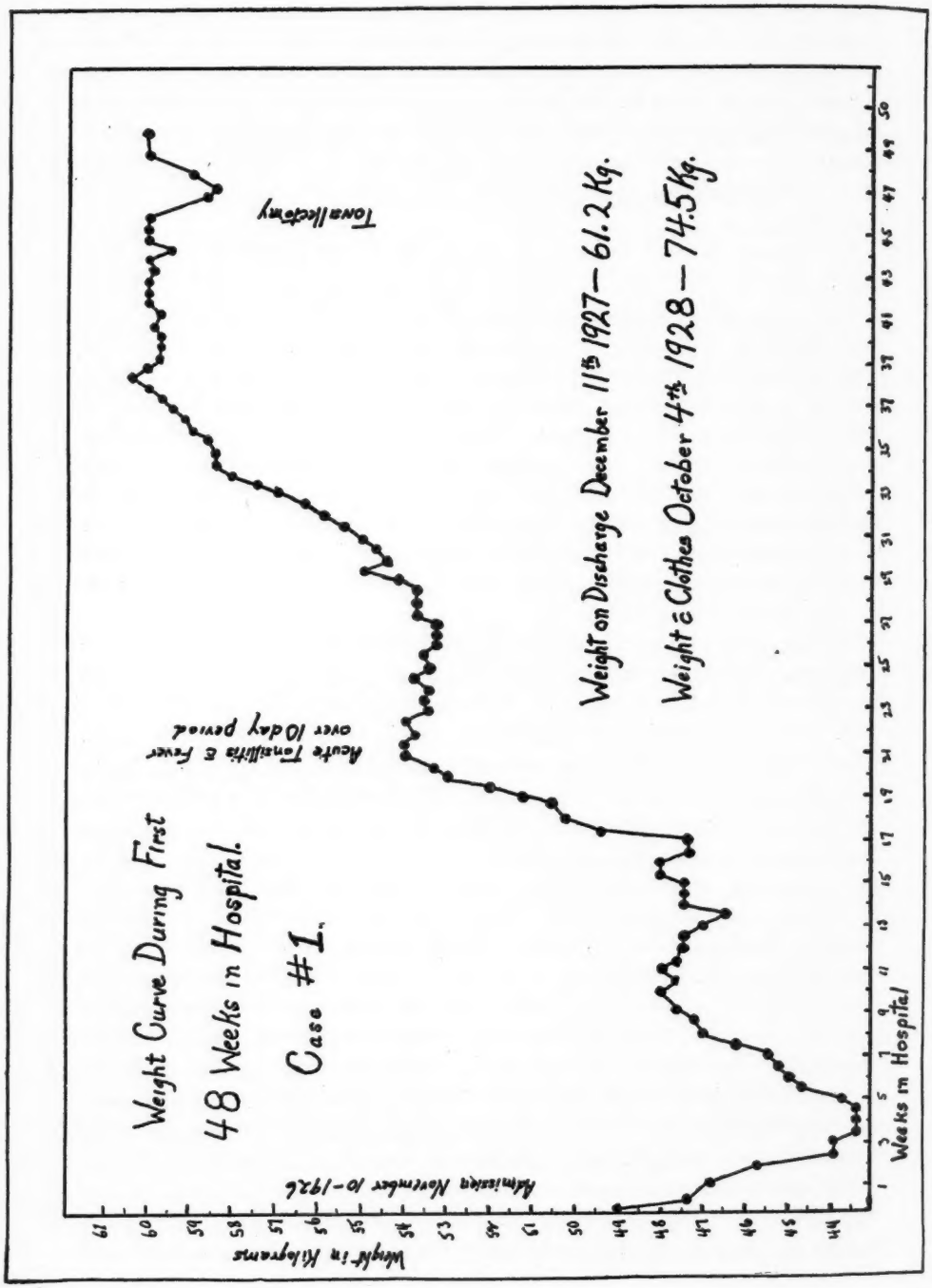
It may well be stated that the number of cases cited is not imposing, but one need only point out the indefinite character of the disease and the general opinions regarding it. Suggestive physical signs are rarely found; the story is vague; and the medical profession is educated to a belief in the invariable fatality of the condition. Thus, Nothnagel (23) believed that many more cases recover than is realized, because the diagnosis is rarely made if the patient improves. More recently Opie (24) has attempted to call attention to the same idea, emphasizing the fact that cases are not always fatal. With the increasing frequency of more or less routine chest X-rays in some of the larger hospitals, we may expect to find more and more instances of inactive miliary tuberculosis. It is quite possible that not many years hence the prognosis in generalized tuberculosis may be found fairly hopeful in an increasing percentage of cases.

The following two cases are particularly interesting in that one occurred in a negress, and the other was very acute and seemingly hopeless.

Case 1: A 38-year-old negress, P. B. B. H. Med. no. 28,938, was admitted on November 10, 1926, complaining of weakness and loss of weight. There was no family history of tuberculosis and no known association with this disease. Scarlet fever at the age of seven, typhoid fever at fourteen, and influenza at twenty-nine were the only diseases of importance in the past history. An abdominal operation for the removal of a fibroid tumor of the uterus and incidental appendicectomy was performed three years before admission.

The present illness dated from seven months before admission to the hospital. During this time the patient had begun to lose weight, had not as much strength as formerly, and was tired practically all the time. Four months before entry she had worked for five weeks as a servant, but was confined to her bed for one week because of an attack of palpitation. For the past three months she had had a dry, unproductive cough, and had become short of breath on climbing stairs. For a period of eight or nine weeks ending a month before coming to the hospital, she had had night-sweats, and during the last month had felt feverish at night. Nocturia of about twice nightly had developed during the last eight weeks, but micturition was not painful. On admission she had to lie propped up in bed on at least two pillows in order to avoid attacks of coughing. She had lost about 47 pounds in the seven months of the present illness.

Physical examination at the time of admission failed to establish a definite diagnosis. The patient was a well-developed and fairly well-nourished negress lying quietly in bed in no apparent distress. Skull and scalp were not remarkable. Face suggested hyperthyroidism. Hair was streaked with gray. Pupils were normal. There was a slight exophthalmos, but no lid-lag. Ophthalmoscopic examination was negative. Mouth was essentially normal except for slightly enlarged tonsils. Right lobe of the thyroid was palpable, but there were no bruit, thrills, or pulsations. Thorax was symmetrical; respirations were not remarkable. Heart was not enlarged; sounds were of good quality: no murmurs were heard. Blood-pressure was 120/80. Lungs were resonant throughout to percussion. Breath-sounds were normal except for a small area at the left apex where they were a little harsh. A few moist râles were heard in the same area. Fine crepitant râles were heard at the right base posteriorly. Tactile fremitus and vocal fremitus were normal. Lower borders of the lungs moved normally. Abdomen was negative with the exception of a right ventral hernia. No fluid could be made out. There was no lymphadenophathy. The fingers were not clubbed. There was a fine tremor of the extended fingers. Pulse rate was 96; temperature 99.4°. An X-ray, taken in the outdoor department previous to admission, showed a very fine diffuse mottling, uniformly distributed throughout both lungs. The lesions appeared to be of approximately the same age. An X-ray diagnosis


Weight Curve During First
48 Weeks in Hospital.
Case #1.
Acute Tonsillitis & Fever
over 10 day period
Tonsillectomy
Weight on Discharge December 11th 1927 — 61.2 Kg.
Weight & Clothes October 4th 1928 — 74.5 Kg.
Weight in Kilograms
Weeks in Hospital
Admission November 10 — 1926

of miliary tuberculosis was made on November 10, 1926, but the possibility of an accompanying hyperthyroidism was considered.

The patient's course in the hospital covered a period of one year and thirty days, so that it is obviously impossible to give a detailed report of the minute changes. An attempt will be made to mention the more important events which took place in that time. A chart of the weight is a most graphic presentation (chart 1) of the weekly trend of the clinical progress. During the first three weeks in the hospital there was a rapid, steady fall, from 49 to 43.6 kg., although for the most part the temperature was not remarkable, ranging between 98 and 99.6, and the patient was fairly comfortable in bed. From that time the gain in weight was the greatest evidence of improvement. Once established, it was at first fairly rapid, gradually tapering off as a normal weight was attained. Nearly every break in the upward curve of weight represents an attack of tonsillitis, some of which were very severe, with a temperature of 103° or more. Though the local symptoms were usually relatively brief, improvement, as evidenced by the weight-curve, would not follow for a much longer period. The change in the physical signs was very gradual. Râles were heard from time to time, chiefly in the right base and left apex; these were more numerous after the attacks of tonsillitis. Although, for the most part, progress was fairly satisfactory, there were intervals, apart from the periods of sore throat, when the prognosis was far from encouraging. At these times the temperature would be slightly higher and the weight would remain stationary for several weeks.

Stereo X-rays of the chest, taken at monthly intervals, or more frequently, beginning with the first on November 2, were of great benefit in following the case. Variations in the fuzziness of the individual lesions, with other parts of the film remaining sharp to rule out movement, were used as an index of improvement or extension. The general trend was of diminishing size and increasing sharpness of outline, but it was remarkable how accurately the X-ray interpretation would follow the clinical findings. In April, 1927, six months after admission, there was a prolonged febrile period of over four weeks, associated with a sharp break in the climbing weight-curve. An X-ray at that time showed an increase in the size of the individual lesions, with in addition "some consolidation possibly beginning caseation" around the right hilum. The appearance was decidedly worse than at the preceding examination. In May, 1927, the lesions appeared still larger, as if they might be coalescing; the apical lesions were no worse than before. For several months there was little change, and then, following another sore throat, there was an increase in the involvement of the lungs, especially at the bases where the lesions were more confluent, giving almost the picture of a bronchopneumonic phthisis. The next picture, a month later, described the individual lesions as being "smaller and more discrete than those seen on the previous examination."

Shortly after admission a basal-metabolic-rate determination was found to be plus 40 per cent over the average normal. The possibility of a tuberculous infection of the thyroid gland was considered. The patient was obviously not a suitable risk for operation, and nothing was done in the way of specific treatment. Iodine was not considered wise. Subsequent metabolic rates showed a gradual decline until the time of discharge, when a rate of −5 was obtained. The enlargement of the thyroid gland similarly diminished.

During the course of the first six months, attention was called to the appearance of successive crops of cutaneous lesions. These were nodular, intracutaneous, raised, reddened, and slightly tender to palpation. They appeared above the elbows, knees, skin overlying the biceps, middle of the back, and buttocks. The usual development of the lesion began with the discovery of a small lump, which would grow until it reached the size of a small pea or even to 1 cm. in diameter, embedded deeply in the skin. The rather dull red color would then gradually fade; the centre of the lesion would become lighter in color, and in the course of four to six months, the whole thing would entirely disappear. The lesions did not ulcerate. Crops would usually come in association with the general systemic upsets. Biopsy was performed and the pathological report was "tuberculosis of the skin." Repeated examination of the sections stained for acid-fast microörganisms, however, failed to show tubercle bacilli.

In view of the fact that almost all the setbacks had been associated with attacks of tonsillitis of more or less severity, it was decided that an attempt to remove the tonsils under local anaesthesia was justified. Operation was performed on September 30, 1927. It was followed by a febrile period of about five days, the highest temperature of 100.4° having been reached on the second day after the operation. Temperature came down quickly to normal and remained there; there was a weight loss of 1.6 kg. in the ten days of recovery, partially due to fever and partially due to inability to swallow food because of the local trauma of the operation.

The patient recovered fairly quickly from the results of this operation and in October, 1927, eleven months after admission to the hospital, it seemed safe to allow her to leave her bed. Examination of the chest showed that there was "definite dulness of a slight degree over the right base, with the breath-sounds slightly less well heard over this area." No râles were heard. X-ray of the chest showed the lungs definitely clearer than at some of the previous examinations, and the individual lesions appeared smaller and sharper. The films were interpreted as representing a receding miliary tuberculosis. With the mobilization and beginning of light work around the ward, the patient began to complain of dragging pain from the long forgotten ventral hernia. Discomfort was so great that repair under local anaesthesia was advised and carried out on November 2, 1927. Exploration of the abdominal cavity was

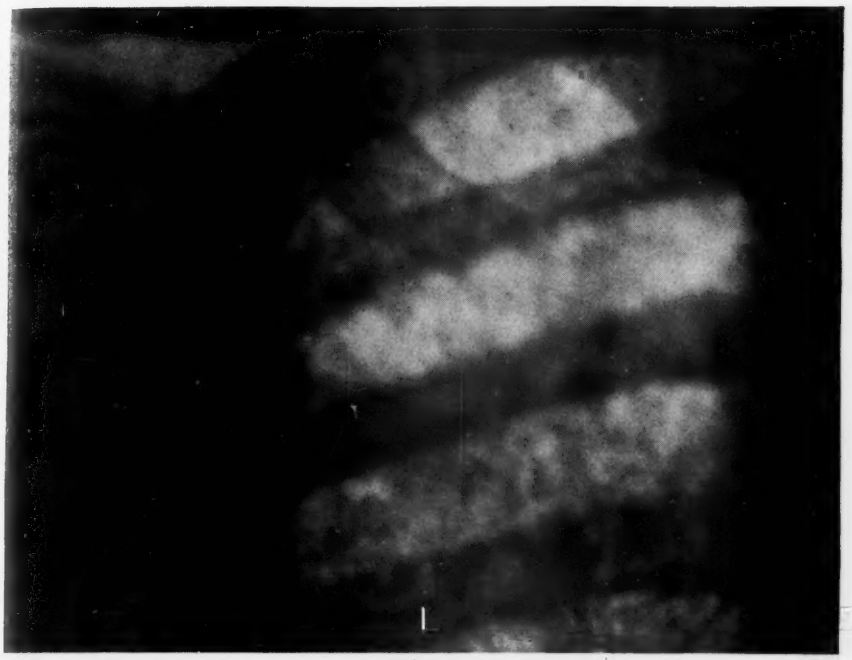
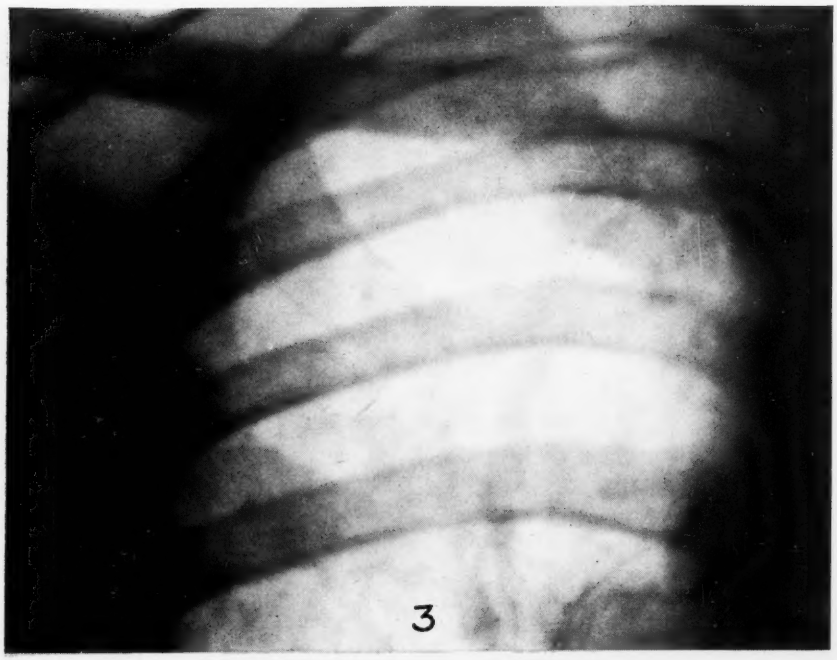


FIG. 1. CASE 1. ON ADMISSION, NOVEMBER 2, 1926
FIG. 2. CASE 1. MAY 19, 1927. AFTER TONSILLITIS



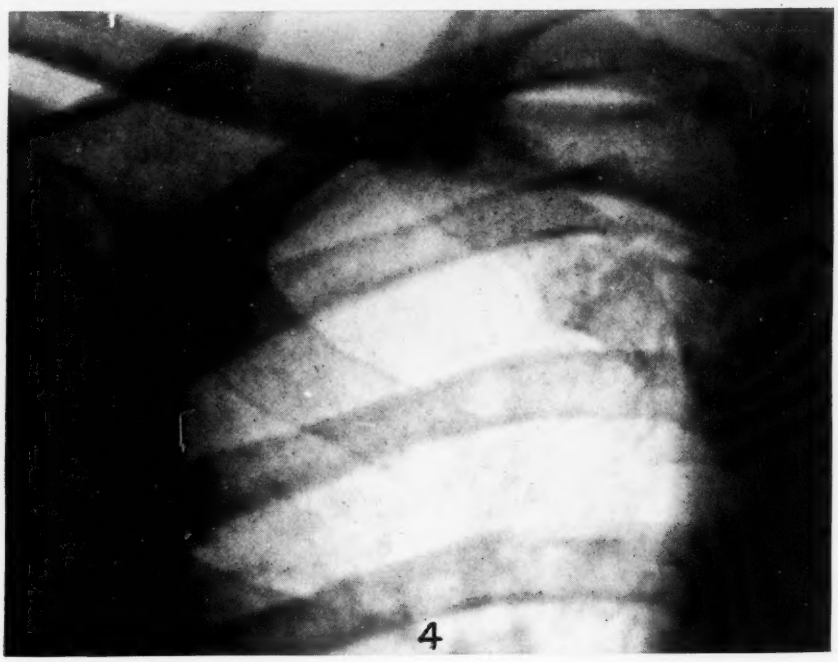


FIG. 3. CASE 1. ON DISCHARGE, DECEMBER 2, 1927
FIG. 4. CASE 1. JUNE 13, 1928

not done, as the patient was too uncomfortable; the intestinal loops exposed in the wound, however, showed no evidence of tuberculosis of the peritoneal cavity. The day following operation there was considerable distention and difficulty in getting her breath, relieved with enemata. The following day her temperature reached 101°, and she developed similar difficulty with respirations because of pain localized in the left chest. Examination showed a very faint friction rub. The pain was relieved by a chest-swathe. Leucocyte count was 17,500 in contrast to the previous level of about 6,000 to 8,000. Convalescence was otherwise uneventful. During the remainder of the stay on the

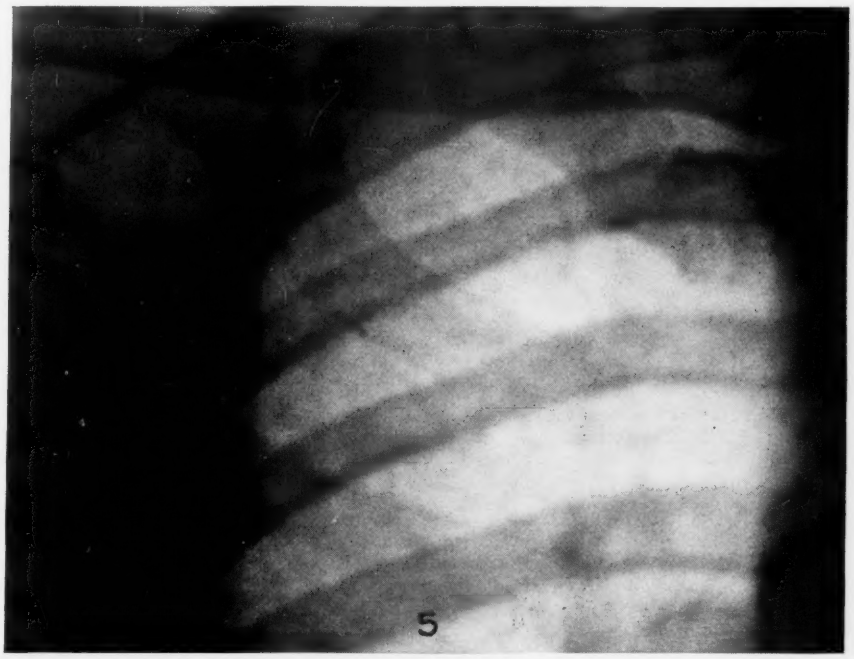


FIG. 5. CASE 1. OCTOBER 10, 1928

ward there was nothing of note in the daily progress. She was discharged on December 11, 1927, weighing 17.6 kg. more than the lowest recorded weight.

Laboratory data obtained during the stay in the hospital may be briefly summarized: Wassermann (blood-serum) negative. Phthalein excretion on November 11, 1926, was 70 per cent in two hours and twenty minutes. Stool normal. Examination of the sputum on ten different occasions showed no acid-fast microörganisms. More examinations were not done, simply because the patient was not raising suitable material. Examination of the urinary sediment at the time of a slight flare-up in the quantity of formed elements

FIG. 6. CASE 1. OCTOBER, 1927
FIG. 7. CASE 1. JULY, 1928

failed to show any acid-fast microörganisms. Urinalysis was consistent with an acute infection early in the course, showing a slight trace of albumin, rare red cells, and a moderate number of granular casts. As the general condition improved and the patient remained afebrile for long periods of time, the urine showed repeatedly no albumin, red cells or casts, and only a rare white blood cell in the uncatheterized specimen. The blood on admission: Hgb. 80 per cent, r.b.c. 4,960,000, w.b.c. 7,050, pmn. 67 per cent, l. 31 per cent, l.m.n. 1 per cent, b.c. 1 per cent. The white blood-count ranged almost continuously between 6,000 and 8,000, except during the attacks of sore throat, when a leucocytosis of about 15,000 was usual. The red-cell counts, made with a certified pipette in the month previous to discharge, were all between 6,020,000 and 6,100,000 cells. Whether this polycythaemia was due to diminished aeration of the lung, it is impossible to say.

Since discharge from the hospital the patient has remained well and has been followed in the outdoor department with frequent examinations and X-rays of the chest. She continues to feel well, has no cough and no recurrence of the cutaneous lesions, and râles have been heard in the chest only once in the ten months since discharge from the hospital. She has gained in weight so continuously that it has been necessary to limit her intake of food. In February, 1928, X-ray of the chest showed only a faint ghostly mottling of the lungs, the individual lesions being hardly perceptible. And again in June there was only a moderate diffuse mottling in the lower half of the right lung with a suggestion of the miliary appearance previously noted. The lungs elsewhere were not remarkable. The patient was last seen in October, 1928. She had attempted to do full-time work, but was overtired and returned to relative inactivity. The resulting pain low in the back and frequency of urination disappeared after a week's rest. She had no symptoms except easy fatigability. Her lungs, on physical examination, showed no variation from normal. There had been no further skin involvement. The weight remained about the same as before. A new X-ray of the chest is interpreted as showing still more clearing, as well as evidence of calcification of the individual lesions.

Case 2: The patient was a 38-year-old Austrian, P. B. B. H. med. no. 30365, who was admitted to the P. B. B. H. on June 12, 1927, complaining of chills and fever. His family history and past history are irrelevant. Venereal disease was denied, and there was no known exposure to tuberculosis. A year previous to admission, after a chilling and exposure, he first began to have pain in the lower abdomen. Beginning at that time and continuing to the time of entry, he had urinary frequency of about once every three-quarters of an hour. There were also some urgency and burning on micturition. He had not felt well since the onset of these symptoms. Two months before admission, for a period of three or four days, he had a chill every morning followed by fever. These chills

recurred two weeks preceding entry, coming one very evening at about seven-thirty o'clock, and being associated with chattering teeth and a rise in temperature. He also had severe drenching night-sweats. During this two weeks the genitourinary symptoms were also more severe. When seen by his local doctor his temperature was 103° and 104° on two occasions. No abnormal physical signs had ever been found in his chest previous to entry.

Physical examination on admission was that of a fairly healthy young man. The tonsils were slightly inflamed; the heart questionably enlarged but not otherwise abnormal; the lungs were clear, no râles being heard even after coughing. Examination of the admission specimen of urine showed numerous acid-fast microörganisms. Several days later X-ray of the chest revealed no evidence of pulmonary tuberculosis, although the hilum shadows and lung markings were slightly increased. Fluroscopy was negative. Cystoscopy resulted in the diagnosis of tuberculosis of the right kidney and bladder, stained smear and guinea pig both showing the presence of acid-fast microörganisms. The left ureteral orifice was normal. Phthalein excretion on the left was good, and there were no leucocytes in the specimen from the ureteral catheter.

The patient was transferred to the surgical service, and on June 18th the right kidney was removed under gas-oxygen anaesthesia. The pathological diagnosis was tuberculosis of the kidney. A right-flank incision was made and the kidney exposed retroperitoneally. Dissection was difficult owing to swollen oedematous tissues. The peritoneum was torn anteriorly, plugged with gauze, and later repaired. In emptying the kidney by trocar, considerable material escaped into the perirenal tissues, resulting later in a good deal of drainage around the rubber-tissue wick. About an ounce of pus was expressed from the upper pole of the wound about a week after the operation, but for the most part the patient's progress was satisfactory. His temperature was tending toward normal, and he was gradually being allowed to sit up. Five weeks after the operation, there was a fairly sharp temperature rise, followed by a picket-fence type of fever, reaching 102° and 103° every evening. At this time, X-ray of the chest showed a fine diffuse mottling of the lungs, fairly uniform, more apparent in the right lung than in the left. The lesions were all of the same size. The findings were considered typical of miliary tuberculosis. The patient then decided that he was not getting any better in the hospital and insisted on going home against advice. On August 4th, arrangements were made through the social-service department for his care at a convalescent home, but he is reported to have stayed only a short time.

In September, 1928, more than a year after discharge, it was learned that the patient was well enough to continue his work as a laundryman. An attempt was made to have him return to the hospital for further study, but this was met with absolute refusal. He was persuaded to have an X-ray of the chest, which shows the previous lesions in the lungs to be smaller and

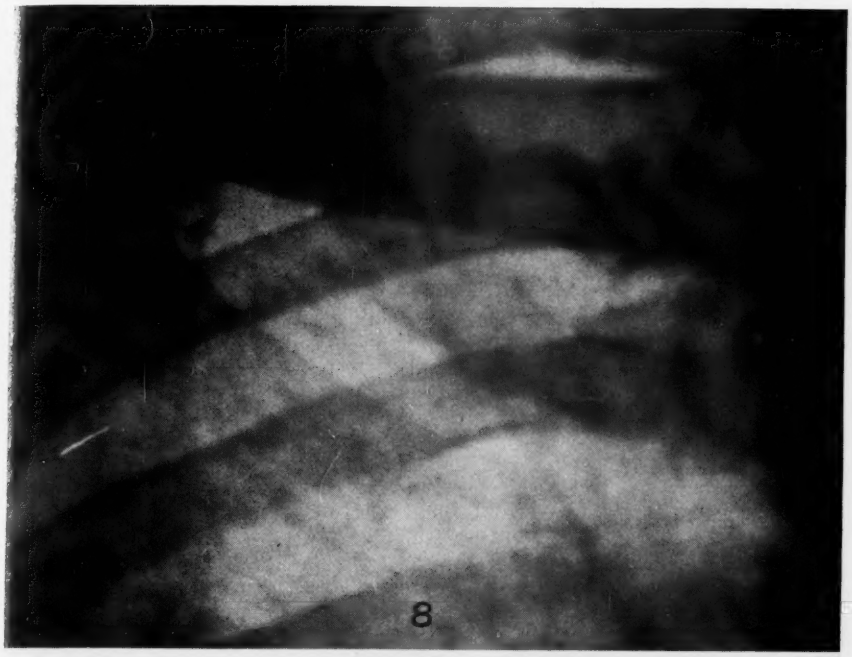


FIG. 8. CASE 2. AUGUST 1, 1927
FIG. 9. CASE 2. SEPTEMBER 13, 1928

more discrete, with no evidence of activity. No information was available from the patient, but his wife reports that although he is working he is not well. The wound is said to be closed at present, but there is a bulging area which still occasionally discharges. No definite story of the symptoms was obtainable.

CONCLUSION

In conclusion it may be well to state that the first case is presented in the knowledge that the diagnosis of miliary tuberculosis is not absolutely proved, though, with the appearance of the lungs by X-ray and the typical pathological lesion of tuberculosis in one of the excised skin lesions, the evidence seems to be so overwhelmingly in favor of such a diagnosis that it seems fully justifiable to call attention to it as a further indication that miliary tuberculosis may not always be a hopeless situation. The second case is admittedly far from well, but, from what is known of him, the local lesion is apparently of more importance than the general one. In this patient there was the same X-ray appearance of the lung, regarded as typical of miliary tuberculosis, and also the demonstrated tuberculosis of the kidney. So far as I have been able to determine, both cases have passed the limit of duration of all the reported cases seen during the active stages of the disease. Moreover, they are noteworthy in that other evidences of tuberculous activity have been demonstrated during the course of the miliary tuberculosis. It is hoped that a later report will be possible in both instances.

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THE GRAPHIC METHOD FOR THE BLOOD-SEDIMENTATION TEST[1,2]

Presentation of a 1-cc. Technique and Other Important Modifications and Suggestions

JACOB CUTLER

The blood-sedimentation test is one of the newer laboratory procedures striving for a place as a valuable diagnostic aid and prognostic index in infectious and destructive diseases. Although known to physicians for centuries and at one time considered a particularly important clinical sign, both theoretically and practically, its present popularity is due to Fahraeus (1), who, in 1918, introduced it as a diagnostic aid in early pregnancy. More than six hundred and fifty articles have appeared in the literature since. Many of the early claims have been modified or discarded. To-day, no one thinks of the sedimentation test as an early diagnostic procedure in pregnancy or in any disease entity, for the sedimentation reaction is nonspecific.

Evidence is accumulating to show that in the final analysis the sedimentation phenomenon depends upon the amount of cellular destruction going on in the body. As the blood circulates from part to part it carries away products of tissue destruction which alter its stability. In healthy individuals, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, and although this varies from day to day it remains within limits considered normal. Even this relatively small amount of tissue destruction is registered by the sedimentation test. This was clearly shown by Greisheimer (2), who made 174 repeated observations on a group of 31 healthy men and women and observed that the sedimentation rate varied from week to week in the same individual but always within normal limits.

Should the amount of tissue destruction pass beyond the normal, then the stability of the blood becomes altered and the red blood cells settle out quickly from the plasma. All the observations recorded in recent litera-

[1] From the Eagleville Sanatorium, Eagleville, Pennsylvania.

[2] Read before the Pathological Society at the College of Physicians, Philadelphia, Pennsylvania, January 10, 1929.

ture emphasize this important fact: that regardless of the disease present, whether it be active pulmonary tuberculosis, malignant tumor, pelvic inflammatory disease, acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of that disease.

It becomes evident, therefore, that the sedimentation reaction portrays a disturbed physiology of the blood, resulting from destructive disease, and should be looked upon as one of the fundamental phenomena that occurs during disease and regarded as a measure of pathological activity in the same sense as fever or leucocytosis. It is often more to be depended upon than subjective or objective findings. This does not mean that the sedimentation test is to replace any established procedure or to force to the background sound clinical judgment. On the contrary, if this test be used in conjunction with temperature chart, blood findings, physical examination, history and clinical judgment, it will often cast an additional ray of light upon a complex problem and make for greater confidence in the handling of the sick. The sedimentation test should therefore be welcomed.

A MULTIPLICITY OF TECHNIQUES

One of the confusing things about the sedimentation test is the multiplicity of techniques. This is not surprising since the test is still in its developmental stage. Many of the techniques described, however, are simply modifications and not new procedures employing new principles. Generally speaking, there are three methods for performing the blood-sedimentation test: the time, the distance, and the graphic methods, depending upon the manner in which the results are recorded, whether in distance (millimetres), time (minutes), or graphs. Practically every technique described in the literature, when classified, will fall into one of these groups.

The distance method is the oldest and was first advocated by Fahraeus. It has been modified by numerous others, but the Westergren (3) modification has met with most favor. Its underlying principle is noting the distance through which the red blood cells sediment in a fixed time and recording the result in millimetres. Westergren employs pipette tubes, 300 mm. in length and 2.5 mm. internal diameter, with a mark 200 mm. from the bottom of the pipette (figure 1). The pipette is filled with citrated blood up to the 200-mm. mark and the blood allowed to sediment.

The height of the supernatant fluid column is measured at the end of one hour, two hours and twenty-four hours, and the results expressed in millimetres. The one-hour reading is the most important and furnishes the basis for comparison. Normal readings at the end of one hour are, for men, 1 to 3 mm., and for women, 4 to 7 mm.

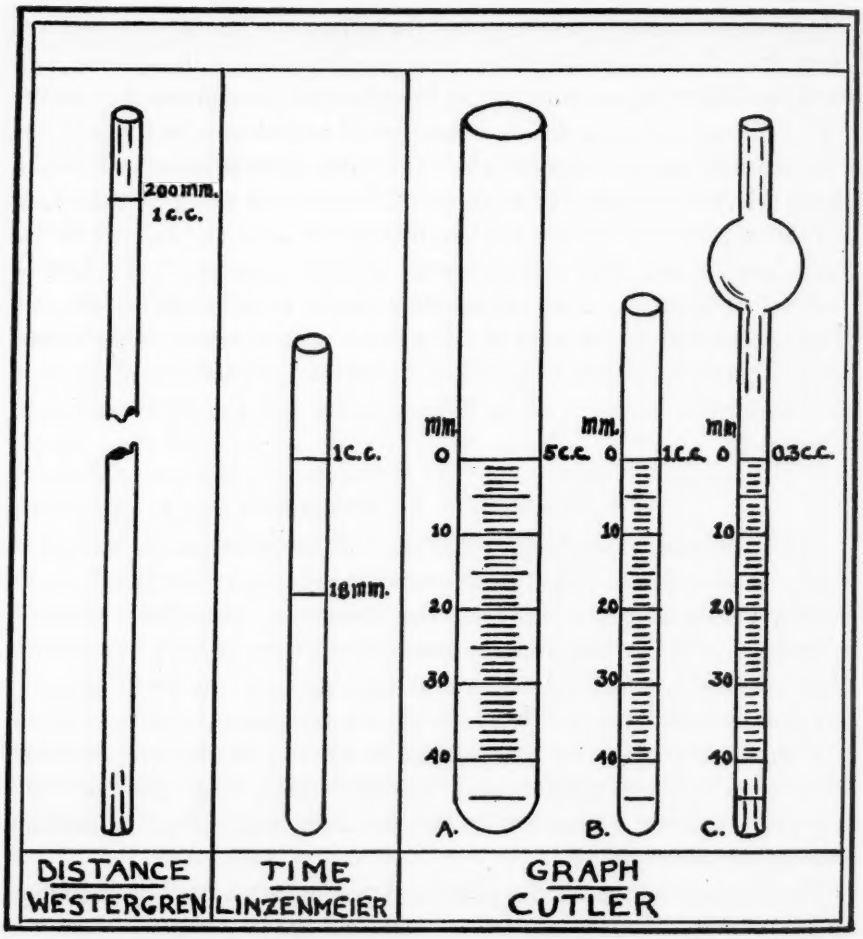

FIG. 1. PRINCIPAL METHODS OF SEDIMENTATION TEST

The time method of studying the sedimentation reaction, as devised by Linzenmeier (4), is the direct opposite of the distance method. In the distance method one fixes the time and measures the distance through which the red cells sediment, recording the results in millimetres, while in

the time method one fixes the distance and observes the time, recording the results in minutes.

The Linzenmeier technique is as follows: Glass tubes, 6.5 cm. long and 5 mm. internal diameter, are used (figure 1). These are scaled at the 1-cc. level and at 18 mm. below the 1-cc. mark. The speed with which the sedimenting erythrocytes reach the 18-mm. mark serves as the basis of comparison, and constitutes what is known as the sedimentation time. One hundred and twenty minutes (2 hours) is the generally accepted lower level of normal readings.

While there are numerous modifications of both the time and distance methods, they are of little importance and do not help to simplify matters. Most of them have to do with the size of the tube, degree of dilution and amount of blood used. All of them either fix the distance and measure the time, or fix the time and measure the distance. Fischel (5), Morris (6), and Rubin (7) and others measure the distance as usual, but, instead of recording the results in absolute figures, express them in percentages of the whole blood column.

THE GRAPHIC METHOD

The graphic method, as the name implies, expresses its results graphically and has been described by me in detail in a previous communication (8). Its essential features are as follows: Sedimentation tubes of 5-cc. capacity are used, graduated into tenths of a cc., each one millimetre in height and marked in millimetres (*A*, figure 1). The graduations begin with zero at the 5-cc. level and increase downward to fifty. One-half of one cc. of 3 per cent sodium-citrate solution and 4.5 cc. of blood, obtained by puncture of a suitable vein, are gently mixed in a syringe and poured into the tube. The position of the sedimenting column of erythrocytes is determined every five minutes for one hour. The observations are recorded on charts (figure 2) which have been designed for that purpose, on which the horizontal lines represent the divisions on the tube and the vertical lines the intervals of time. Graphs are then constructed, which not only show the position of the sedimenting column of erythrocytes at any period of time during the first hour, but also portray the changes in velocity that occur during the process of sedimentation.

FOUR DISTINCT GRAPHS

Carrying out the sedimentation test in this manner it will be seen that there are four distinct graphs, two of which are straight lines, and two,

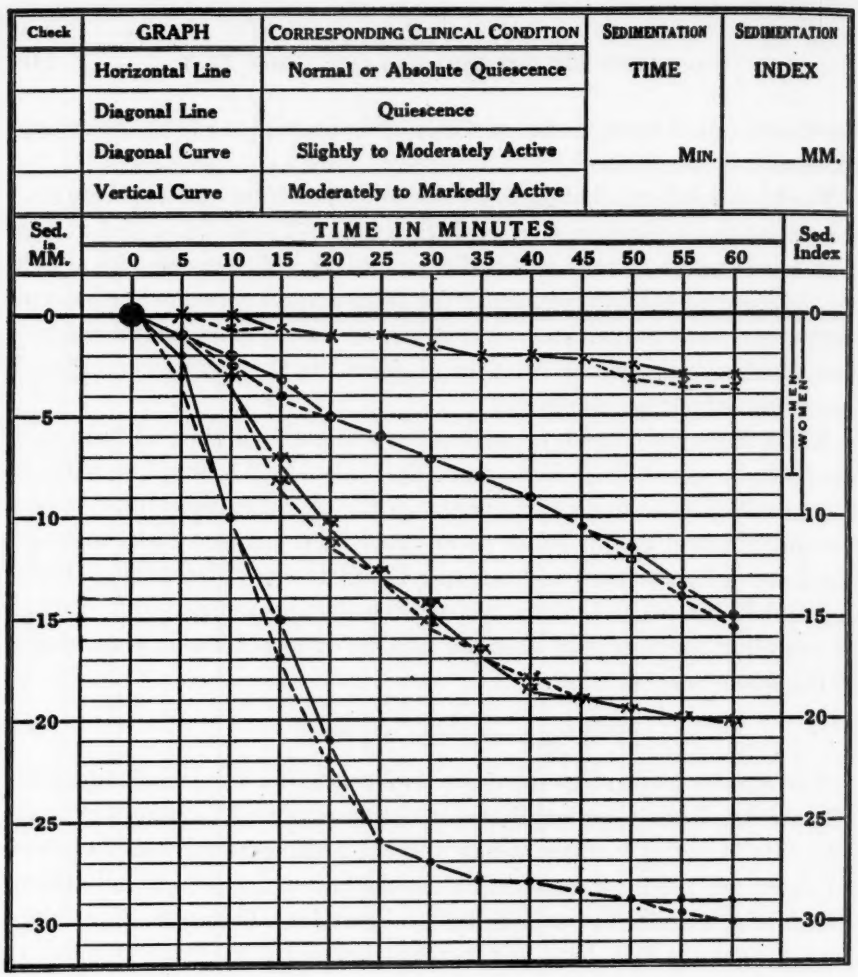

FIG. 2. REVISED SEDIMENTATION CHART. COMPARISON OF GRAPHS AS OBTAINED WITH 5-CC. AND 1-CC. METHODS

--x--x--
—x—x— } Horizontal line (clinically healthy individual)

--0--0--
—0—0— } Diagonal line (clinically quiescent tuberculosis)

--xx--xx--
--xx--xx-- } Diagonal curve (clinically slightly active tuberculosis)

—.—.—
—.—.— } Vertical curve (clinically markedly active tuberculosis)

———— Graph obtained with 1-cc. method
———— Graph obtained with 5-cc. method

curves. From their physical appearance I have named them horizontal line, diagonal line, diagonal curve and vertical curve. The horizontal line is a normal finding and indicates absence of active destructive disease. It does not, however, exclude the presence of such disease, if it be inactive. The sedimentation test merely records the disturbance in the stability of the blood produced by the absorption of products of tissue destruction, and when there is not sufficient tissue destruction the sedimentation test is normal. The horizontal line, therefore, may indicate one of two things: either health, or the presence of destructive disease not sufficiently active to disturb the natural stability of the blood.

The diagonal line, diagonal and vertical curves are always abnormal findings and always indicate different degrees of the intensity of the destructive process.

THE SEDIMENTATION INDEX

For a complete evaluation of the sedimentation test, one must determine two factors in addition to the graph, namely, the sedimentation index and the sedimentation time. These bring out the finer details of the sedimentation reaction and help to determine the degree of activity or quiescence. In this way they make possible the comparative study of apparently similar graphs.

The sedimentation index represents the total sedimentation of red blood cells at the end of sixty minutes expressed in millimetres. It is directly proportional to the severity of the infection, becoming greater as the infection becomes more active and vice versa. The normal sedimentation index for men may vary from 2 to 8 mm. with an average of 3 to 4; for healthy women from 2 to 10 mm. with an average of 5 to 6. Under pathological conditions it may reach as high as 35. Its real value lies in evaluating horizontal and diagonal lines, and in that way revealing hidden but important information.

THE SEDIMENTATION TIME

The sedimentation time requires a little more explanation but is not difficult to understand.

If blood from a healthy individual is allowed to settle, settling takes place very slowly and is complete within 5 to 15 hours. Graphically, it is represented by a straight line.

If inflammatory blood is allowed to settle, sedimentation occurs rapidly and may be complete within 15 to 20 minutes, depending upon the sever-

ity of the infection. Graphically, it is represented by a diagonal or vertical curve. If one studies the vertical curve in figure 2, portraying, as it does, rapid sedimentation, it will be seen that the sedimentation phenomenon may be divided into three stages: first, a period of slow sedimentation; second, a period of rapid sedimentation; and third, a period of packing when the sedimentation slows again, and finally comes to a natural standstill because the corpuscles have become packed in the bottom of the tube. The time that elapses before this period of packing sets in represents the time required for the practically complete settling of the erythrocytes, and is known as the sedimentation time.

Care must be taken not to confuse this definition of the term with that used by Linzenmeier. They stand for two entirely different things. In the Linzenmeier technique it is an arbitrary finding, depending upon the speed with which the sedimenting erythrocytes reach the 18-mm. level. In my technique the sedimentation time represents a stage in the natural process of sedimentation and means just what its name implies: the number of minutes that elapse before the period of packing of the red cells sets in.

What the sedimentation index is to the horizontal and diagonal lines, the sedimentation time is to the diagonal and vertical curves. It evaluates and differentiates between apparently similar graphs and in that way reveals data which ordinarily would be lost. Generally speaking, the sedimentation time is inversely proportional to the severity of the infection, becoming shorter as the infection becomes more active and vice versa. Clinically, it is of value when reduced to sixty minutes or less. After that it yields no information which cannot be obtained from the horizontal or diagonal line and sedimentation index.

I have adopted the following rule for accurately determining the sedimentation time: I note on the chart, when the curve begins to flatten out, at what period of time the settling of the erythrocytes in five minutes was one millimetre or less. The first time when that occurs determines the onset of the period of packing and also the sedimentation time. Thus the sedimentation time for the diagonal curve in figure 2 is 45 minutes, and for the vertical curve, 30 minutes. The sedimentation time also differentiates between border-line diagonal and vertical curves. If the sedimentation time is 35 to 60 minutes, the graph is a diagonal curve; if the time is 30 minutes or less, it is a vertical curve. When the graph is a horizontal or diagonal line sedimentation as a rule is not complete within sixty minutes, and the sedimentation time, therefore, is not recorded.

All study of the test is complete at the end of one hour. I have studied the sedimentation reaction in over 150 cases every five minutes for the first hour, every ten minutes for the second hour, every fifteen minutes for the third hour and also at the end of twenty-four hours, and I am convinced that nothing can be gained by making a single observation after sixty minutes.

INTERPRETATION OF TEST

The interpretation of the sedimentation test by the graphic method can be best illustrated by quoting the conclusions which I reached after carefully studying the sedimentation test in pulmonary tuberculosis (8). These conclusions I also find true in other infectious processes, such as peritonitis, salpingitis, septicemia and pneumonia. I hope to present these studies in the near future.

In healthy individuals and in tuberculous individuals in whom the disease has become absolutely quiescent, the graph is normal, that is, it is a horizontal line.
In tuberculous individuals, in whom the disease is not absolutely quiescent but who do not have sufficient pathologic activity to develop constitutional symptoms, the graph is usually a diagonal line but with a variable sedimentation index which is directly proportional to the degree of pathologic activity.
In tuberculous individuals in whom the pathologic activity is such that constitutional symptoms develop, the graph obtained is usually a diagonal or vertical curve, but with a variable sedimentation time which is inversely proportional to the severity of the infection.
Diagonal curves are obtained chiefly in clinically slight to moderately active tuberculosis, while vertical curves are obtained chiefly in clinically moderately to markedly active tuberculosis.

THE 1-CC. TECHNIQUE

In the original graphic technique, described in my first contribution, I used a sedimentation tube of 5-cc. capacity. Further study, however, convinced me that, within reasonable limits, the quantity of blood used makes little difference. The important thing is to keep the height of the blood column constant. This observation was corroborated by others, notably by Fischel. It was the utilization of this principle which enabled me to perfect the finger-puncture method (9) (*C*, figure 1) and which also makes it possible for me to present the following 1-cc. technique, to which I wish to call particular attention.

Essential Apparatus[3]

1: One-cc. Cutler sedimentation tubes. These tubes have an internal diameter of 5 mm. and are marked in millimetres, beginning with zero at the 1-cc. level and increasing downward to 50 (*B*, figure 1).

2: Sedimentation racks for carrying and reading sedimentation tubes (figures 3 and 4). The reading rack is constructed to enable the observer to read fifteen tubes at the same time with complete visibility of each tube.

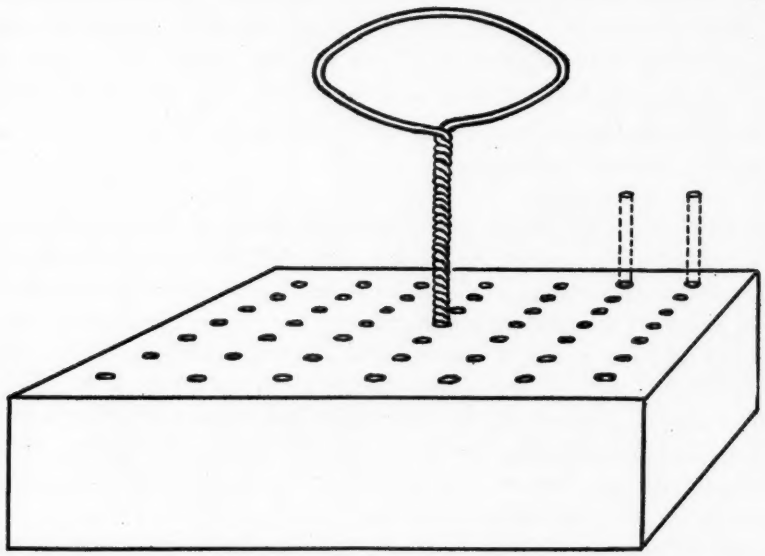

FIG. 3. CARRYING RACK, CAPABLE OF HOLDING 48 SEDIMENTATION TUBES

3: Cutler sedimentation charts for recording observations (figure 2). This chart represents a distinct improvement over the one originally published.

4: One- or 2-cc. syringe, graduated into 0.1 cc. and 20-gauge needle for drawing blood.

Procedure

Cleanliness and dryness of apparatus are essential. If any clotting occurs, the test must be repeated. Before puncture of the vein, aspirate into the syringe 0.1 cc. of 3 per cent freshly prepared sterile sodium-citrate

[3] All the apparatus may be obtained from the Arthur H. Thomas Company, Philadelphia, and the charts from John Hartenstine, Norristown, Pennsylvania.

solution, to prevent clotting of blood. Draw the blood up to the 1-cc. mark, and gently mix blood and citrate solution by tilting syringe back and forth, after drawing in a little air. Pour contents into the sedimentation tube and allow tube to stand in carrying rack until ready to make readings. Each tube is numbered to prevent error.

When ready to start readings, each tube should be stoppered with a paraffine-coated cork, inverted and gently tapped against the palm of the hand. This procedure is repeated three or four times to ensure uniform distribution of the red blood cells. If this part of the technique is neglected, there will not be uniform distribution and the readings will be misleading and worthless.

The test is read by noting the position of the sedimenting column of red blood cells every five minutes for one hour. This is done with ease,

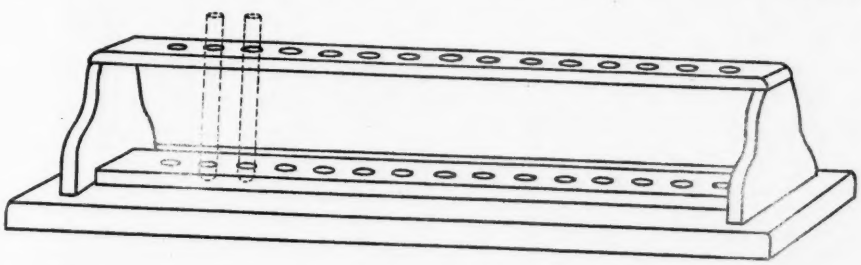

FIG. 4. SEDIMENTATION RACK, CONSTRUCTED TO ENABLE THE OBSERVER TO READ 15 TUBES AT THE SAME TIME WITH COMPLETE VISIBILITY OF EACH TUBE DURING SEDIMENTATION

as the boundary zone between the red blood cells and the plasma is usually sharp and distinct. The observations are recorded on the sedimentation charts, on which the horizontal lines represent the divisions on the sedimentation tube and the vertical lines the intervals of time. A graph is then constructed.

In many instances it will be sufficient to observe the position of the sedimenting column of red blood cells every five minutes for thirty minutes, then at forty-five and sixty minutes, respectively, thus reducing the number of essential readings to eight. The most important and striking changes always occur during the first thirty minutes.

The sedimentation value is determined according to the path traversed by the red blood cells during the first hour and depends upon the nature of the graph, sedimentation index and sedimentation time, and is the same as when the 5-cc. method is used.

TABLE 1

Comparative results of 5-cc. and 1-cc. methods, both tests made simultaneously upon each patient. Figures in first line opposite case number are for 5-cc. method, serving as a control, and in second line for 1-cc. method

CASE NUMBER	GRAPH				SEDIMENTATION INDEX	SEDIMENTATION TIME	CASE NUMBER	GRAPH				SEDIMENTATION INDEX	SEDIMENTATION TIME
	Horizontal line	Diagonal line	Diagonal curve	Vertical curve				Horizontal line	Diagonal line	Diagonal curve	Vertical curve		
					mm.	*minutes*						*mm.*	*minutes*
1	x/x	...	...	...	1/1	...	21	...	x/x	...	...	12/12	...
2	x/x	...	...	...	3/3.5	...	22	...	x/x	...	...	12/12	...
3	x/x	...	...	...	4/5	...	23	...	x/x	...	...	12/12	...
4	x/x	...	...	...	4/5	...	24	...	x/x	...	...	12/10	...
5	x/x	...	...	...	4/2	...	25	...	x/x	...	...	12.5/13	...
6	x/x	...	...	...	4.5/3.5	...	26	...	x/x	...	...	14/12	...
7	x/x	...	...	...	5/6	...	27	...	x/x	...	...	16/15	...
8	x/x	...	...	...	5/6	...	28	...	x/x	...	...	17/19	...
9	x/x	...	...	...	5/4	...	29	...	x/x	...	...	18/19	...
10	x/x	...	...	...	5/7	...	30	...	x/x	...	...	18/18	...
11	x/x	...	...	...	6/8	...	31	...	x/x	...	...	18/21	...
12	x/x	...	...	...	6/7	...	32	...	x/x	...	...	18/20	...
13	x/x	...	...	...	6.5/6	...	33	...	x/x	...	...	18/20	...
14	x/x	...	...	...	7/7	...	34	...	x/x	...	...	18.5/20	...
15	x/x	...	...	...	7/8.5	...	35	...	x/x	...	...	18.5/20	...
16	x/x	...	...	...	9/10	...	36	...	x/x	...	...	19/23	...
17	x/x	...	...	...	9/7	...	37	...	x/x	...	...	19/16	...
18	x/x	...	...	...	10/9	...	38	...	x/x	...	...	19/21.5	...
19	x/x	...	...	...	10/10	...	39	...	x/x	...	...	20/17	...
20	...	x/x	...	...	11.5/12.5	...	40	...	x/x	...	...	20/20	...

TABLE 1—*Concluded*

CASE NUMBER	GRAPH				SEDIMENTATION INDEX	SEDIMENTATION TIME	CASE NUMBER	GRAPH				SEDIMENTATION INDEX	SEDIMENTATION TIME
	Horizontal line	Diagonal line	Diagonal curve	Vertical curve				Horizontal line	Diagonal line	Diagonal curve	Vertical curve		
					mm.	*minutes*						*mm.*	*minutes*
41	...	x/x	...	...	21/22	...	61	...	...	x/x	...	23/20	40/55
42	...	x/x	...	...	21/22	...	62	...	...	x/x	...	23/23	40/35
43	...	x/x	...	...	21.5/22	...	63	...	...	x/x	...	23/23	40/40
44	...	x/x	...	...	22.5/22.5	...	64	...	...	x/x	...	23/23	40/40
45	...	x/x	...	...	22.5/23	...	65	...	...	x/x	...	25/27.5	40/50
46	...	...	x/x	...	22/21	60/50	66	...	...	x/x	...	25/25	40/40
47	...	...	x/x	...	24/23	55/50	67	...	...	x/x	...	27.5/26	40/40
48	...	...	x/x	...	24/24.5	55/50	68	...	...	x/x	...	28/26	40/35
49	...	...	x/x	...	20/20	50/55	69	...	...	x/x	...	28/27	40/40
50	...	...	x/x	...	21/19	50/45	70	...	...	x/x	...	21/22	35/35
51	...	...	x/x	...	22/20	50/40	71	...	...	x/x	...	22/20	35/45
52	...	...	x/x	...	22/22	50/40	72	...	...	x/x	...	22/25	35/35
53	...	...	x/x	...	23/23	50/50	73	...	...	x/x	...	25/27	35/40
54	...	...	x/x	...	23/21	50/55	74	...	...	x/x	...	27/27	35/35
55	...	...	x/x	...	23.5/23	50/50	75	...	...	x/x	...	27.5/27	35/35
56	...	...	x/x	...	23.5/24	50/50	76	...	...	x/x	...	28/25	35/35
57	...	...	x/x	...	22/24	45/35	77	...	...	...	x/x	26/29	30/30
58	...	...	x/x	...	24/22	45/45	78	...	...	...	x/x	29/30	30/30
59	...	...	x/x	...	24/21	45/50	79	...	...	...	x/x	29/26	30/30
60	...	...	x	x	29/27	45/30							

Figure 2 and table 1 show the comparative results obtained by the 5-cc. and 1-cc. methods. Both tests were made simultaneously upon each patient, the 5-cc. technique serving as a control in each instance. It will be noticed that the 1-cc. method parallels the 5-cc. method very closely, and that the differences that occur here and there are of minor importance and do not interfere with a practical interpretation of the result. The character of the graph, which is the all essential feature, is the same.

When it is necessary that the sedimentation test be carried out in hospitals under routine conditions, the following modification, if adopted, would make it unnecessary to puncture the vein as a special procedure for the sedimentation test:

Draw the blood in the usual manner for all studies desired. Pour 0.9 cc. of this sample of blood into the sedimentation tube, into which has been previously placed 0.1 cc. of 3 per cent sodium-citrate solution. Gently invert tube two or three times to ensure uniform mixing of blood and citrate solution. The remainder of the technique is the same as described.

The 1-cc. technique is a desirable modification. When the sedimentation test has to be repeated at frequent intervals, the small amount of blood withdrawn and the negligible pain produced because of the small-calibre needle used are of importance in helping to overcome prejudice and fear on the part of the patient. Other advantages also suggest themselves, such as the greater ease with which the sample of blood may be obtained in difficult cases, especially in nervous individuals. I prefer the 1-cc. technique to the 5-cc. and finger-puncture methods.

ADVANTAGES OF THE GRAPHIC METHOD

Since the sedimentation test has so many possibilities and is making such a strong bid to become one of our trustworthy laboratory aids, it is only fair to request that it should not be hampered by a multiplicity of techniques. It is hoped that the following advantages of the Cutler method over those in general use will convince many, who are interested in the blood-sedimentation test, to use this method.

1: It is scientific: The sedimentation reaction is studied as a natural phenomenon from beginning to end and not within the confines of arbitrary limits.

2: It is complete: It is the only method which permits of a complete study of the sedimentation reaction as it actually occurs in the sedimentation tube, by recording the changes in the velocity of sedimentation at

regular time intervals. It is this change in velocity which is the most valuable and most informative part of the test. This is completely lost in the time and distance methods, or their modifications. All study only one phase of the reaction, the end-result. This is perhaps the least important of all the observations that can be made.

3: It is delicate: It is the most delicate method that has so far been devised. By means of the graph, sedimentation index and sedimentation time, it reveals all the possible information that the sedimentation reaction can yield.

4: The interpretation is simple: The horizontal line is a normal finding and indicates either health or the absolute quiescence of destructive disease. The diagonal line, and diagonal and vertical curves are abnormal findings and always indicate different degrees of intensity of the destructiveness of the disease.

5: It is graphic: The results are presented graphically and leave a lasting impression on the mind. Improvement or lack of improvement can be dramatically visualized by recording subsequent sedimentation-test findings upon the original chart. As the patient improves the graph should approach more and more the horizontal line, but, should he become worse, more and more the vertical curve.

6: It is time-saving: No observations are made beyond the first hour. In all, only eight readings are essential. As many as twenty-five tests can be studied by the same individual at the same time with comfort and interest. Since the greatest use of this test is in its clinical application, speed, without sacrifice of accuracy and correct interpretation, is manifestly an asset.

7: It is available under all conditions: The test may be carried out either by puncturing the vein or the finger tip. Venipuncture may be done with either 5 cc. or 1 cc. of citrated blood. The finger-puncture method requires less than 0.3 cc. of blood. These methods are interchangeable, studied in the same manner and give practically identical results, thus making the sedimentation test available under all conditions. Of these the 1-cc. technique is the simplest and easiest.

8: It is easy: With the 1-cc. technique described in this article, the sample of blood required can easily be obtained. To read the test only the average amount of careful observation is required, as the line of demarcation between the plasma and the sedimenting column of red blood cells is usually clear and distinct. This means that the average individual can perform the sedimentation test with no special training and little difficulty.

SUMMARY

The blood-sedimentation test is rapidly proving itself of clinical value as a diagnostic aid and prognostic index in infectious and destructive diseases. It reflects the disturbance produced in the blood through the absorption of products of tissue destruction and serves as a measure of such destruction regardless of aetiology.

A new technique for the study of the sedimentation test is described. This technique utilizes the graphic method of presentation developed by Cutler and requires 1 cc. of citrated blood. Many suggestions are offered to simplify and clarify this method. Its advantages over those in the literature are definitely pointed out and a plea is made for the adoption of a standard technique.

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THE RELATIONSHIP BETWEEN BLOOD-SEDIMENTATION INDEX AND FIBRIN CONTENT IN TUBERCULOUS INDIVIDUALS

ESTHER M. GREISHEIMER, CHARLOTTE C. VAN WINKLE AND OLGA H. JOHNSON[1]

The relationship between the sedimentation rate and the fibrin content in tuberculous individuals has not been investigated to any extent. A report of the relationship in relatively normal individuals has been given in another publication (1).

The rate of sedimentation of blood cells in tuberculosis has been the subject of numerous reports. Von Muralt (2) in 7 cases of pulmonary tuberculosis found a rapid rate of sedimentation in the severe cases. Cutler (3) introduced a graphic method of study, and found the rate of sedimentation a good index of the degree of activity. Wrenn (4) in more than 300 cases of pulmonary tuberculosis found that the sedimentation rate ran parallel to the degree of anatomical involvement. He gave a good review of the previous work, and considered the graphic method superior to the others. Peers (5) found a relationship between the degree of activity and the sedimentation rate, as did many others (6) (7) (8).

Rubin (9) and Hubbard (10) have recently called our attention to the importance of the cell count in the sedimentation rate (not on tuberculosis patients). Undoubtedly this will have to be considered in future work, although in a previous study (11) there seemed to be no relationship between the blood count and the rate of sedimentation.

Since so little has been done on the relationship between the sedimentation rate and the fibrin content in tuberculous individuals, the present work has been directed along that line.

RESULTS

All of the studies in this report were made on tuberculous adults residing in Glen Lake Sanatorium. The sedimentation index was de-

[1] Department of Physiology, University of Minnesota, and Glen Lake Sanatorium, Oak Terrace, Minnesota.

termined by the Cutler method, using 0.5 cc. of potassium oxalate (4.4 per cent) instead of citrate. Readings were made at 15, 30, 45 and 60 minutes. The fibrin was then determined on the plasma of the same sample, by the Wu colorimetric method, with slight modifications. We found it necessary to keep the phenol reagent in a cool dark place. It was freshly made each month. At one time the tenth-normal hydrochloric acid (used for making the tyrosine standard) showed a growth developing in it. Tyrosine, dissolved in this acid, kept its strength a relatively short time. The contaminated acid was discarded, and

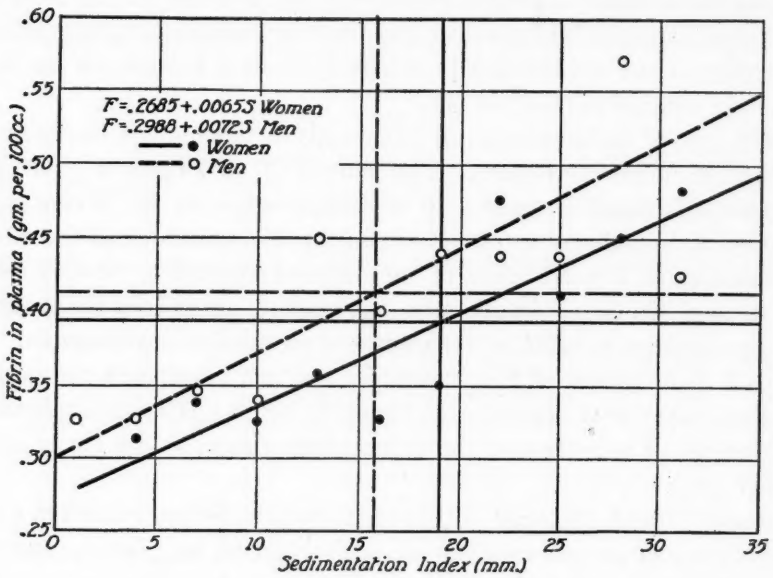

CHART 1

tyrosine made with a fresh solution of hydrochloric acid retained its original strength several months. All of the fibrin determinations were made in duplicate.

1. Entire Group of Each Sex

The series included 101 women and 138 men, ranging in age from 18 to 83 years. The average sedimentation index for women was 19.18 ±.55 mm.; the average index for men was 15.89 ±.50 mm. The difference between the sexes is 3.29 ±.74 mm. The difference is 4.4 times as large as its probable error, and is probably significant. The average fibrin content of the plasma in women was .3936 ±.0061 gm. per 100 cc.;

for men it was .4127 ±.0064 gm. The difference between the sexes is .0191 ±.0088 gm. Since the difference is 2.2 times as large as its probable error, it may be significant.

The usual statistical methods have been employed. For advice in connection with the use of these methods we are greatly indebted to Prof. J. Arthur Harris. A study of the relationship between fibrin content and the sedimentation index gave a correlation coefficient, r_{FS}, of .595 ±.043 for the women. (F = gms. of fibrin per 100 cc. of plasma and S = the sedimentation index in mm.) This is 13.8 times as large as its probable error.

The linear regression equation, calculated from the means, standard deviations, and correlation coefficient is $F = .2685 + .0065\ S$, where, as above, F = grams of fibrin per 100 cc. of plasma, and S = sedimentation in mm. The empirical mean fibrin contents as ordinates are plotted against the sedimentation indices in the graph (chart 1).

The correlation coefficient, r_{FS}, for the men was .567 ±.039. This is 14.5 times as large as its probable error. The linear regression equation is $F = .2988 + .0072\ S$. The empirical mean fibrin contents as ordinates are plotted against the sedimentation indices in the graph.

The difference between the correlation coefficients of the two sexes is .028 ±.058. Since the difference is only a fraction of the probable error, it cannot be considered significant. Thus it appears that the correlation is essentially identical in the two sexes.

2. Investigation of Women of Different Ages

In the foregoing results the findings for the women as a whole were presented. The group will now be analyzed into 3 smaller groups, according to age. The subgroups will include women between 18 and 28, 29 and 39, and 40 and 50 years. This particular grouping is used in order to facilitate comparison with the study of relatively normal individuals (1). The results for each subgroup are presented in table 1.

It will be observed in table 1 that the index increases gradually with age, while the fibrin decreases with age. The correlation is significant in every group.

The deviations of the index, fibrin content, and correlation coefficient for the subgroups, classified according to age, from the comparable constants for the group as a whole are shown in table 2. These differences are taken [constant for subgroup] less [constant for entire group], in order to give signs which will show whether the constants for the subgroups are larger or smaller than those for the entire group.

As seen in table 2, the index is smaller in the 18–28 year group, and larger in the other two groups, than in the group as a whole. The fibrin content is larger in the 18 to 28 and 29 to 39 year groups, and smaller in the 40 to 50 year group than in the group as a whole. The correlation coefficient is larger in each subgroup than in the group as a whole.

Certain prepublication criticisms were made to the effect that the one-hour reading (index) was inadequate for determining the relationship between fibrin content and sedimentation rate. To determine

TABLE 1

Tuberculous women. Average index, fibrin content, and correlation coefficient of each subgroup, and the entire group

NUMBER	AGE	INDEX		FIBRIN (GRAMS PER 100 CC. OF PLASMA)		CORRELATION COEFFICIENT	
		Average	Range	Average	Range	$r_{FS} \pm$ P.E.	$\frac{r}{\text{P.E.}_r}$
		mm.	*mm.*				
42	18–28	16.78	(4–31)	.4131	(.25–.80)	.673 ±.057	11.8
27	29–39	20.67	(4–37)	.4018	(.25–.60)	.737 ±.059	12.5
24	40–50	21.25	(4–31)	.3646	(.25–.60)	.700 ±.070	10.0
101	18–83	19.18	(4–37)	.3936	(.25–.80)	.595 ±.043	13.8

TABLE 2

Deviations of the index, fibrin content, and correlation coefficient for the subgroups, from the comparable constants for the group as a whole. The entire group figures are the subtrahends

AGE	DEVIATION OF INDEX	DEVIATION OF FIBRIN CONTENT	DEVIATION OF CORRELATION COEFFICIENT
18–28	−2.40	+.0195	+.078
29–39	+1.49	+.0082	+.142
40–50	+2.07	−.0290	+.105

whether the index gave reliable data in respect to this relationship, coefficients of correlation between the fibrin content and the 15-, 30-, and 45-minute readings for the entire group were calculated. The results are presented in table 3. The sedimentation in mm. at each time interval, the coefficient of correlation between the fibrin content and the amount of sedimentation, and the difference between the coefficients so found and the one-hour coefficient are given. The latter serves as the subtrahend in each case.

It is shown in table 3 that the correlation between sedimentation rate and fibrin content has about the same values in the 15-, 30-, and 45-minute readings as in the one-hour reading.

A study of the relationship between index and age in the tuberculous women gave a correlation coefficient, r_{AS}, of .211 ±.064. (A = age in years and S = sedimentation in mm.) This is 3.3 times as large as its probable error.

A study of the relationship between fibrin content and age in the tuberculous women gave a correlation coefficient, r_{AF}, of −.225 ±.064. (A = age in years and F = grams in fibrin per 100 cc. of plasma.) This is 3.5 times as large as its probable error.

TABLE 3

Results of 15-, 30- and 45-minute readings for tuberculous women

TIME	SEDIMENTATION	CORRELATION COEFFICIENT		CORRELATION COEFFICIENT DIFFERENCES	DIFFERENCE / P.E. DIFFERENCE
		r_{FS} ± P.E.	$\frac{r}{\text{P.E.}_r}$		
	mm.				
15 minutes	6.109	.503 ±.050	10.1	−.092 ±.066	1.4
30 minutes	12.703	.562 ±.046	12.2	−.033 ±.063	0.5
45 minutes	16.475	.616 ±.042	14.6	+.021 ±.060	0.3

TABLE 4

Tuberculous men. Average index, fibrin content, and correlation coefficient of each subgroup, and the entire group

NUMBER	AGE	INDEX		FIBRIN (GRAMS PER 100 CC. OF PLASMA)		CORRELATION COEFFICIENT	
		Average	Range	Average	Range	r_{FS} ± P.E.	$\frac{r}{\text{P.E.}_r}$
		mm.	mm.				
45	18–28	11.33	(1–28)	.4311	(.20–1.00)	.694 ±.052	13.3
28	29–39	17.29	(4–31)	.3893	(.25– .65)	.586 ±.084	6.9
30	40–50	17.90	(1–31)	.3917	(.30– .50)	.745 ±.055	13.5
27	51–61	19.44	(7–28)	.4389	(.30– .60)	.810 ±.045	18.0
138	18–83	15.89	(1–31)	.4127	(.20–1.00)	.567 ±.039	14.5

3. Investigation of Men of Different Ages

The results for the men as an entire group have already been presented. The group will now be divided into 4 subgroups, according to age. These subgroups will include men between 18–28, 29–39, 40–50 and 51 to 61 years. The results for each subgroup are presented in table 4.

Table 4 shows an increase in the sedimentation index with age. The fibrin content first decreases, then increases. The correlation is significant in every group.

The deviations of the index, fibrin content, and correlation coefficient

for the subgroups, classified according to age, from the comparable constants for the group as a whole are shown in table 5. As with the women, these differences are taken [constant for subgroup] less [constant for entire group], in order to give signs which will show whether the constants for the subgroups are larger or smaller than those for the entire group.

Table 5 shows a smaller index in the 18 to 28 year group and a larger index in the other three groups than in the group as a whole. Similar results were found in the women. The fibrin content in the 18 to 28 and 51 to 61 year group is larger, while that in the other two groups is smaller,

TABLE 5

Deviations of the index, fibrin content, and correlation coefficient for the subgroups, from the comparable constants for the group as a whole. The entire group figures are the subtrahends

AGE	DEVIATION OF INDEX	DEVIATION OF FIBRIN CONTENT	DEVIATION OF CORRELATION COEFFICIENT
18–28	−4.56	+.0184	+.127
29–39	+1.40	−.0234	+.019
40–50	+2.01	−.0210	+.178
51–61	+3.55	+.0262	+.243

TABLE 6

Results of 15-, 30- and 45-minute readings for tuberculous men

TIME	SEDIMENTATION	CORRELATION COEFFICIENT		CORRELATION COEFFICIENT DIFFERENCES	DIFFERENCE / P.E. DIFFERENCE
		$r_{FS} \pm$ P.E.	$\frac{r}{\text{P.E.}_r}$		
	mm.				
15 minutes	4.913	.555 ±.040	13.9	−.012 ±.056	0.2
30 minutes	10.283	.598 ±.037	16.1	+.031 ±.054	0.6
45 minutes	13.717	.495 ±.043	11.5	−.072 ±.058	1.2

than in the group as a whole. The correlation coefficient is larger in each subgroup than in the group as a whole.

The correlation coefficients for the 15-, 30- and 45-minute readings for the entire group of men are presented in table 6. The sedimentation in mm. at each time interval, the coefficient of correlation between the fibrin content and the amount of sedimentation, and the difference between the coefficient so found and the one hour coefficient are given. The latter serves as the subtrahend in every case.

The correlation is significant, as shown by table 6, at the various time intervals studied. It does not differ significantly from the one-hour correlation.

A study of the relationship between index and age in the tuberculous men gave a correlation coefficient, r_{AS}, of .295 ±.063. (A = age in years and S = sedimentation in mm.) The coefficient is 4.7 times as large as its probable error.

A study of the relationship between fibrin content and age in the tuberculous men gave a correlation coefficient, r_{AF}, of −.048 ±.057. (A = age in years and F = grams of fibrin per 100 cc. of plasma.) The coefficient is smaller than its probable error.

SUMMARY AND CONCLUSIONS

1. The sedimentation index (Cutler graphic method) in a series of 101 tuberculous women averaged 19.18 ±.55 mm.; in 138 tuberculous men it averaged 15.89 ±.50 mm. The difference between the two sexes is 3.29 ±.74 mm. This difference is probably significant. Similar differentiation exists in relatively normal men and women (1).

2. The fibrin content (Wu colorimetric method) for tuberculous women averaged .3936 ±.0061 gm. per 100 cc. of plasma. For tuberculous men the average was .4127 ±.0064 gm. The difference between the two sexes is .0191 ±.0088 gm. This difference may be statistically significant. This is in agreement with the result found on relatively normal individuals (1).

3. The correlation coefficient, r_{FS}, between fibrin content and sedimentation index is .595 ±.043 for the tuberculous women and .567 ±.039 for the tuberculous men. Both show a significant relationship between fibrin content and sedimentation index. The agreement of the constant for the two sexes is excellent.

4. The average index increased from 16.78 ±.81 mm. in the 18 to 28 year group to 21.25 ±1.17 mm. in the 40 to 50 year group of tuberculous women. The difference between the highest and lowest age group is 4.47 ±1.42 mm. The difference is 3.1 times as large as its probable error. The coefficient of correlation (r_{AS}) between index and age is .211 ±.064.

The average sedimentation index increased from 11.33 ±.81 mm. in the 18 to 28 year group to 17.90 ±.99 mm. in the 40 to 50 year group of tuberculous men. The difference between these groups is 6.57 ±1.28 mm. The difference is 5.1 times as large as its probable error.

The coefficient of correlation (r_{AS}) between index and age is .295 ±.063. The results for the males and the females are in good agreement.

5. The average fibrin content decreased from .4131 ±.010 gm. in the 18 to 28 year group to .3646 ±.011 gm. in the 40 to 50 year group of

tuberculous women. The difference is .0485 ±.015 gm. The difference is 3.2 times as large as its probable error. The coefficient of correlation (r_{AF}) between fibrin and age in the tuberculous women is −.225 ±.064.

In tuberculous men the average fibrin content varied irregularly. It was .4311 ±.015 gm. in the 18 to 28, .3893 ±.013 gm. in the 29 to 39, .3917 ±.0066 gm. in the 40 to 50, and .4389 ±.012 gm. in the 51 to 61 year group. If we compare the 18 to 28 and the 40 to 50 year groups, as in the women, we find a decrease of .0394 ±.016 gm. This difference is 2.4 times as large as its probable error.

The coefficient of correlation (r_{AF}) between fibrin and age in tuberculous men is −.048 ±.057. The results for men and women differ materially in the correlation between fibrin content and age. Explanations for this difference cannot be given until a larger group of tuberculous women from 51 to 61 years of age is studied. The required number is not available at Glen Lake.

6. In both the entire group, of both sexes, and also in each subgroup, a significant relationship is found between the fibrin content and sedimentation index.

7. In both sexes, a significant correlation exists between the fibrin content and the amount of sedimentation determined in 15-, 30- and 45-minute, as well as in 1-hour periods.

We desire to express our gratitude to Profs. J. Arthur Harris and Clarence M. Jackson for valuable criticism in the preparation of the manuscript.

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PROTECTIVE INOCULATION AGAINST TUBERCULOSIS WITH BCG[1]

A. CALMETTE AND HARRY PLOTZ

In a recent article (1), published in THE AMERICAN REVIEW OF TUBERCULOSIS, S. A. Petroff, Arnold Branch, and William Steenken, Jr., communicate the results of their researches on the biological characteristics of a strain of *BCG*. These workers report on the possibility of dissociating this culture into two types of colonies,—one termed *R* (rough) which is nonvirulent, and the other *S* (smooth) which is virulent for the guinea pig. They also claim to have been able, under special conditions, to transform the type *R* into the type *S*, and they conclude that, while the *BCG* strain is only slightly virulent, it may nevertheless rarely produce active tuberculosis in the guinea pig and the rabbit. It is their opinion that, because of its possible danger, the *BCG* vaccine should not be employed in man.

We wish herewith to present our objections to the communication cited, and leave it to the reader to appraise the merits of a method which is now employed with success in Europe and in South America.

We will not discuss the conditions under which Petroff and his coworkers carried on their experiments, but it should be pointed out that a a possible source of error might have occurred, because of the possibility of a spontaneous tuberculous infection occurring in guinea pigs raised in a locality where the tubercle bacillus is so widely disseminated. As a matter of fact, Henry Sewall (2) calls attention to this possibility. We are then not surprised to observe the results of Petroff's inoculations of animals, some of which were surely infected previously with a human strain of tubercle bacilli, which reacted so irregularly to the inoculation of the same original strain of *BCG*. It should be observed that the results published by Petroff and his coworkers are in complete disaccord with the numerous experiments carried on at the Pasteur Institute of Paris, the Robert Koch Institute of Berlin, by R. Kraus and Gerlach in Vienna, by A. Ascoli in Milan, by Zlatogoroff and Tzeknowitzer at

[1] Bacillus Calmette-Guérin.

Kharkoff, by Silbersmith in Zürich, by Lyle S. Cummins at Cardiff, and C. Chagas at Rio de Janeiro.

In none of these various laboratories has any observer reported upon the development of fatal tuberculosis in an animal inoculated with the *BCG* strain. It has occurred that animals, inoculated subcutaneously, intraperitoneally or intravenously with very large doses of *BCG*, developed large caseous lesions, and subsequently died because of the disorder caused by them, but in no instance did a reinoculation of these products (pus or caseous material) into a normal animal produce a progressive lesion. It has been definitely shown that the reinoculation of the products produced by the inoculation of a large dose of *BCG* is not transferable to new animals. This is contrary to what is always observed with virulent tubercle bacilli.

On the other hand, we cannot help but be surprised that the inoculation of the *S* colony into rabbits produces only a benign osteoarticular lesion,—a lesion which presents all the characteristics following the inoculation of the human type of bacillus. But it should be recalled that the original culture of *BCG* is a bovine strain, which was isolated by Nocard from the udder of a tuberculous cow and that the bovine characteristics of this strain have never changed.

According to what Petroff reported at the International Conference on the *BCG*, held at Paris, it appears that he finds about one *S* colony to about 50,000 *R*-type colonies in the same culture. In other words, one milligram of *BCG*, which contains about 40 million bacilli, should contain at least 800 virulent bacilli. If this were true, then all the guinea pigs inoculated subcutaneously or intraperitoneally with one milligram of *BCG* should die of a rapid generalized tuberculosis. But we know definitely that this does not occur. Even the inoculation of one centigram of *BCG*, subcutaneously or intravenously, produces only a local or visceral lesion, which heals spontaneously, is never reinoculable, and never results in fatal tuberculosis.

It appears then that there must be some error in the conclusions reported by Petroff and his coworkers. As far as we are able to ascertain, no worker has been able to confirm their results. Attempts made, not only by ourselves, but by R. Kraus, A. Ascoli, Cantacuzene, Tzeknowitzer, Kirchner, Bruno Lange, etc., have constantly been negative.

Furthermore, contrary to Petroff's conclusions, no one has been able to augment the virulence of the *BCG*, either by successive passage in susceptible animals, or by testicular inoculation in guinea pigs. None of

the many attempts to "induce a return of virulence" for the *BCG* has been successful, whether by reducing the vitamines in the animals, by producing an intoxication or infection by bacterial toxins or mineral poisons (phosphorus), or by an added bacterial infection (streptococcus).

We must then conclude, with R. Kraus, that the *BCG* has become a fixed, hereditarially attenuated strain, quite like the Pasteur antianthrax vaccines.

The International Conference, called by the Medical Section of the League of Nations, held at Paris in October 1928, has expressed an opinion regarding the *BCG.* The bacteriologists, who were members of this Conference,[2] were unanimous in affirming the innocuousness of *BCG* for animals. All the clinicians and veterinarians[3] (with the single exception of Nobel of Vienna) concurred in this opinion, and furthermore stated that the *BCG* had definite immunizing properties.

These conclusions now cannot be doubted after the vast experience obtained in various different countries, namely, France, Russia, Belgium, Spain and Norway.

While the statistics published by one of us in 1927 were criticized, because they were not established according to the rules laid down by professional statisticians (Greenwood, Rosenberg), still those published since can hardly be criticized, for they refer to children vaccinated at birth, and to nonvaccinated subjects, all of whom were born and brought up in tuberculous families, and were followed over a period of four years. It has been shown that the mortality from all causes among the nonvaccinated children (birth to 4 years) was 21.4 per cent (of which 15.9 per cent were tuberculous), while the mortality from all causes among the vaccinated children was only 11.8 per cent (of which 3.4 per cent were tuberculous). These figures were obtained from 2,368 vaccinated and 4,854 nonvaccinated children from 1 to 4 years, all born and brought up in tuberculous surroundings.

It has been shown further that, whenever vaccination with the *BCG* has been systematically practised over a period of years, as was done in certain French and Rumanian cities, the general mortality was diminished to about one-half, and sometimes to two-thirds. This is evidence that the *BCG* is efficacious and inoffensive. The harmlessness of the vaccine may be judged from the following: In France alone,

[2] Ascoli, Berger, Bordet, Cantacuzene, Fraenkel, Gerlach, Kraus, Neufeld, Nowak, Remlinger, Tzeknowitzer, Vallée, Zeller.

[3] Leon Bernard, Heimbeck, Nobel, Ronzoni, Sayé, Schlossmann.

132,000 children have been vaccinated from July, 1924, to January, 1929. In no instance has a deleterious effect following the use of the vaccine been noted. The same results were observed in Rumania, where in the city of Bucarest alone 8,000 infants received the *BCG* at birth.

It should be recalled that, before this method was applied to man, its protective properties had been demonstrated by a considerable amount of experimentation, in particular the work carried on in 1923 on anthropoid monkeys in Guinea by R. Wilbert (3) (recently confirmed by F. Gerlach (4) on the *Macacus rhesus* in Vienna) and a vast experience on cattle, which to-day amounts to more than 10,000 head in various countries (France, Belgium, Holland, Russia, Italy, Brazil, Canada).

We do not feel that we are going beyond the limit of prudence in suggesting that the *BCG* vaccine should be extensively employed, especially when we are dealing with infants born and brought up in suspected or in tuberculous families. The vast experience already gained should justify this opinion. At any rate, it would be advantageous to follow the example of William H. Park and his coworkers, who for more than two years have been following the results of vaccination with *BCG* in New York. Up to the present they have observed no accidents and have been satisfied with their results.

METHOD OF VACCINATION WITH BCG

The technique of vaccination as applied to the newborn is very simple. One-half hour before feeding, the infant is given by mouth a dose of one centigram of a fresh culture of *BCG*, which has been finely emulsified in a liquid which conserves the vitality of the bacilli (synthetic Sauton medium, diluted one-fourth in distilled water). It is convenient to give this emulsion in a small amount of warm milk. The ingestion of the vaccine is repeated twice at 48-hour intervals. The total amount of vaccine taken is 3 cgm. of bacilli.

The vaccination should be carried on during the first ten days of life, for it is during this period that the intestine is better able to absorb the bacteria. Later, when the intestinal mucosa is developed, absorption is much poorer and quite irregular.

It is important that the bacterial emulsion employed as a vaccine should be made from a young culture, one no older than 25 days, so that the vaccine should contain the greatest number of living bacteria. Dead bacteria do not vaccinate, or confer only a slight resistance to a virulent infection.

The vaccinated child should be, as far as possible, separated from its tuberculous mother for a period of four weeks, the necessary period to obtain an immunity. When this separation is not possible, as may happen, it is necessary to take the greatest precaution to prevent a massive infection during the first month.

This oral vaccination leads to no physiological disturbance, no rise in temperature, and no general reaction. It is readily taken by all infants, even those born prematurely. There seems to be no doubt that the ingested bacilli are absorbed, for they may be found in the lymph nodes, weeks or months later, in children that have died by accident or from nontuberculous infections. The vaccinated infants, even though separated from all contagion, react to tuberculin, that is, develop an allergic reaction, after a period of a few weeks or months. But this allergic reaction is not indispensable for the establishment of an immunity, that is, a resistance to reinfection. The allergic reaction is only developed when the vaccine produces the formation of a few giant cells, which are reabsorbed and soon disappear, without leaving any trace of their presence.

We should not then consider the presence of a tuberculin allergic reaction as necessary for the establishment of an immunity. But when it does exist it indicates that the subject is immune.

The allergic reaction should be provoked, however, in children of all ages, as well as in adults, when it is not present, and when its absence cannot be explained by some physiological or pathological reason (eruptive diseases, exposure of skin to sun, menstruation, etc.).

The *BCG* is the best method of inducing this reaction. For this purpose it should be given subcutaneously, in one inoculation, employing 1/40 to 1/20 of a milligram, depending upon the age. This should only be employed in subjects in whom the absence of the allergic reaction has been determined by the Pirquet or intracutaneous procedures, after two tests, at an interval of one week.

Vaccination by the subcutaneous method is now employed on a large scale in a number of countries, particularly in Norway, and in Africa among the colored population. This inoculation is absolutely inoffensive and produces a tuberculous allergic reaction in from 6 to 8 weeks. These inoculations may well be repeated several times during the life-time of the individual, especially in infancy and adolescence, and particularly if the allergic reaction disappears. The use of this method should no doubt greatly reduce the ravages of tuberculosis in the near future. It is, therefore, desirable that clinicians become acquainted with its use.

Fresh vaccinating emulsions of *BCG* may now be obtained in all countries. The Pasteur Institute of Paris has given and continues to give the original strain, when asked for by public-health authorities or by governments. Only one request is made, namely, that the vaccine should not be employed commercially, and that its use should be controlled by the public-health authorities in each country. All precautions are then taken to assure those that wish to employ this new method for the prevention of tuberculosis.

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COEXISTENT SYPHILIS AND TUBERCULOSIS[1]

ADOLPH L. GALLANT[2]

Special interest in simultaneously occurring syphilis and tuberculosis was stimulated by virtue of a relatively high percentage of positive Wassermann reactions found in carrying out routine blood tests at the Robert Koch Hospital. It has been contended for some time that a Wassermann reaction may at times give false positives when the cholesterinized antigen is employed in tuberculosis. Stucky and Huntley (1) believe this is to be due to a "cross-fixation" of complement between tuberculosis and syphilis, since in both these diseases lipoid antigens are used in the complement-fixation test. Newham (2) states that leprosy, scarlet fever, malignant diseases of the liver, kala azar, and African tick fever have all been reported at times as giving a positive Wassermann reaction, but he believes at the same time that it is difficult to rule out concurrent syphilis. Broeman (3) contends that a positive hloesterinized antigen alone, with no history or clinical signs of the disease, does not mean syphilis. He quotes Stokes upon the too delicate reaction of this antigen, who states, "There is little doubt in my mind that a single antigen test with a highly cholesterinized preparation, while it identifies many concealed infections, will yield a surprising percentage of false positives." Engman and Weiss (4) are of the opinion that falsely positive Wassermann reactions occur at times in pregnant women, attributable, they believe, to a hypercholesterinaemia which is often found in pregnancy.

In 1607 cases at the Robert Koch Hospital in which routine Wassermanns were done, 21 per cent were positive. In recent months the Kahn precipitation test has been used in conjunction with the Wassermann test. Of 358 routine Kahn tests 15 per cent were positive. In a vast majority of reports concerning the incidence of concurrent syphilis and tuberculosis, the diagnosis of syphilis has been based on a positive Wassermann reaction alone, the diagnosis resting on laboratory rather than clinical evidence. In the literature there is a variation of from

[1] Read at a meeting of the St. Louis Trudeau Club, St. Louis, Missouri, May 3, 1928.

[2] Robert Koch Hospital, St. Louis, Missouri.

3 to 19 per cent with respect to the frequency of both infections. The diagnosis of syphilis, based purely on the Wassermann reaction alone, or on history alone, is perhaps responsible, according to Habliston and McLane (5), for some of the diversity of opinion in the literature as to the influence of syphilis on tuberculosis. They examined postmortem records of patients in whom both infections were diagnosed simultaneously. About 9 out of 31 cases showed evidence of syphilis at postmortem in which the diagnosis of syphilis was based on the Wassermann reaction alone. Out of 43 cases, 43 showed syphilis at autopsy in which the diagnosis rested on both clinical signs and the Wassermann reaction.

It is the procedure at the Robert Koch Hospital to check a positive Wassermann reaction with another Wassermann, and in recent months with a Kahn test, when there is no clinical evidence of syphilis. If the subsequent test is positive also, the case is classified as one of "latent syphilis." Those cases which present clinical evidence of syphilis and positive serum reactions are classified as "active syphilis" after Habliston and McLane (*loc. cit.*). All the cases in this series of 346 were considered as syphilitic. The difference in the frequency of positive reactions between the Wassermann and Kahn tests was attributed to a certain percentage of falsely positive Wassermann reactions, since the chloesterinized antigen was used. The Kahn test was accepted as specific for syphilis. Stucky and Huntley (*loc. cit.*) conclude that the specificity of the Kahn reaction for syphilis is not affected by the presence of coincident tuberculosis. The small percentage of cases, which were given the benfit of the doubt and classed as syphilitic, will have no effect on the results of this series, because the improvement noted refers to the tuberculosis, and makes the data more striking when this is taken into consideration.

In this study of 346 cases of simultaneously-occurring syphilis and tuberculosis the improvement or lack of improvement in the tuberculosis has been made a basis for determining the efficacy of treating the syphilis in the combined infection. In the statistics presented in this survey 116 cases received treatment for the syphilis and 230 cases did not. Those cases listed under "Treatment" received at least one course of either neoarsphenamin or sulpharsphenamin, and a course of mercury inunctions. No cases were included unless they had received a full course of both arsenic and mercury. A full course of the arsenical consisted of weekly injections of either neoarsphenamin or sulpharsphenamin intravenously, starting with 0.2 gm. for two weeks, then 0.4 gm.

for two weeks, and finally the last two weeks 0.6 gm. Mercury was given by the inunction method, as most of the patients were bedfast. Daily inunctions of 4 gm. (1 dram) of the 30 per cent mercurial ointment for six days, with a bath on the seventh, for six weeks, constituted a course of mercury. These patients received approximately 20 grains of mercury a day by this method. The usual oral hygiene, consisting of an alkaline mouth-wash and strict observation of the urine for signs of mercury poisoning, was carried out. The courses of arsenic and mercury were given simultaneously.

TABLE 1

	Improved	Unimproved	Dead	Total
No treatment (for syphilis).....	48 (20.9%)	51 (22.1%)	131 (57%)	230
Treatment (for syphiis).....	59 (51%)	32 (27.5%)	25 (21.5%)	116

In table 1 the improvement or no improvement refers to the tuberculosis. Quiescent cases, arrested cases, and those cases in which an improvement in symptoms occurred, such as gain in weight, drop in temperature, diminished cough and expectoration, were listed as improved. The cases that remained stationary or grew worse with respect to symptoms were classed as unimproved. It will be noted that the mortality rate was 57 per cent in those cases that received no antisyphilitic treatment. This is the highest mortality rate of any group of cases in the hospital. Under treatment for the syphilis, however, the mortality rate dropped to 21.5 per cent,—a remarkable fact. The average death-rate of the hospital, all cases considered, was 26 per cent for the past year. Consistent with this drop in mortality rate on treating the coexistent syphilis was the rise in improvement from 20.9 to 51 per cent. It is obvious that syphilis coincident with tuberculosis has shown a decidedly unfavorable influence on the tuberculosis, and it is also obvious that treatment of the existing syphilis produces a marked improvement of the tuberculosis. Subdividing these cases according to the extent of their tuberculosis, and using the grouping of the National Tuberculosis Association, that is, Far Advanced, Moderately Advanced, and Minimal, Classes A, B and C, some interesting observations are noted.

TABLE 2

Far advanced

	Improved	Unimproved	Dead	Total
Class C				
No treatment	10	24	114 (77%)	148
Treatment	10	17	20 (42%)	47
Class B				
No treatment	13	15	9	37
Treatment	26	11	2	39

In the Far Advanced, Class C patients, whose syphilis was untreated, 114 out of 148 cases in the group died. This class represents the most active tuberculosis and the greatest involvement of lung. Treating the concurrent syphilis, the death-rate of the class dropped to 42 per cent. In Class B of the Far Advanced cases, representing the same amount of lung involved but a lesser degree of activity of the tuberculosis, the death-rate was lower and the improvement greater with the syphilis untreated than in the corresponding Class C cases, only 9 out of 37 dying, and 13 improved. With treatment of the syphilis in this group only 2 out of 39 died, and 26 improved, with respect to their tuberculosis.

TABLE 3

Moderately advanced

	Improved	Unimproved	Dead	Total
Class C				
No treatment	0	1	2	3
Treatment	0	0	2	2
Class B				
No treatment	16	7	5	28
Treatment	10	4	1	15

In the Moderately Advanced, Class C cases, 2 out of 3 died, and 1 was unimproved, without treatment. With treatment there were 2 cases in this group and both died. This group had very active tuberculosis. In Class B of the Moderately Advanced classification 5 out of 28 died, and 16 out of 28 improved, without treatment for the syphilis. With treatment of the syphilis in this group only 1 out of 15 died, and 10 out

of 15 were improved, Class B cases, it being recalled, having a less active type of tuberculosis.

TABLE 4
Minimal

	Improved	Unimproved	Dead	Total
	Class B			
No treatment	9	4	1	14
Treatment	13 (Class A, (B, C)			13

The Minimal group, Class B, represents the least involvement of lung and moderate activity of the existing tuberculosis. In this group, without treatment, 9 out of 14 were improved and 1 out of 14 died. With treatment, out of 13 cases (Classes B and C) all were improved following treatment for the coexistent syphilis.

From the above statistics it can be seen that treatment of the syphilis combined with tuberculosis will, in an appreciable percentage of cases in which the activity of the tuberculosis is moderate or less, cause a marked improvement in the tuberculosis. This coincides with Potter's (6) conclusion that salvarsan is indicated in latent, chronic and moderately active tuberculosis in which syphilis is also present. Our best results with treatment of the syphilis occurred in the Minimal, Class B, cases in which all of 13 were improved. In this group the amount and activity of the tuberculosis present was at a minimum.

Concerning the treatment of the syphilis in the combined infection, it is the plan to give reduced dosages of the arsenicals, as was stated above. These reduced doses of arsenicals are well tolerated, and in the vast majority of cases no harmful effect has been noted on the tuberculosis. Mercury and the arsenicals were given simultaneously. In a few instances in the Far Advanced active cases there were systemic reactions characterized by chill, pallor, fever, and joint pain, which persisted for a few hours and then subsided with no harmful effect noted. A few very sick and active cases received treatment which apparently made their clinical condition worse, but it must be remembered that a noticeable reduction in the death-rate was obtained in this class of cases, that is, Far Advanced, Class C (77 per cent untreated, 42 per cent treated). We encountered no late arsenic poisoning (hepatitis or

nephritis) nor any cutaneous eruptions (exfoliative dermatitis). Schlomovitz (7) states that both cutaneous and systemic reactions occur more frequently in tuberculosis when the arsenicals are used.

Habliston and McLane (*loc. cit.*) report no bad effects on tuberculosis when the arsenicals are employed. Mauradian (8) states that arsenic is contraindicated in tuberculosis. Jeanselme and Block (9) believe that many patients are benefited by its use and that the tuberculous lesion is not aggravated. Landis (10) is of the opinion that syphilis as an active factor must be removed before any improvement of the tuberculosis can be looked for; he states it is the plan in the combined infection in which the tuberculosis is active to give one-half to one-third the usual dose. Giese and McGovern (11) prefer the arsenicals, and believe there are no contraindications to such treatment after beginning with small doses. Weiss (12) advocates the use of mercury and salvarsan when the two diseases coexist. Terminal stages of tuberculosis with cachexia form contraindications for antisyphilitic treatment according to the *U. S. Venereal Disease Information* (13). This is our belief also. We have seen cases with very active tuberculous disease and high temperature made definitely worse after antisyphilitic treatment. The most beneficial results are to be expected in those cases in which the activity of the tuberculosis is moderate or less and when reduced doses of antispirochaeticides are used.

CONCLUSIONS

1. The coexistence of syphilis and tuberculosis, as based on the Wassermann reaction, has occurred in 21 per cent of the cases treated at the Robert Koch Hospital; as based on the Kahn test the incidence is 15 per cent.

2. Syphilis coincident with tuberculosis has shown a decidedly unfavorable influence on the tuberculosis in direct proportion to the extent and activity of the tuberculosis.

3. Markedly beneficial effects have been obtained by treatment of the syphilis present, especially when the activity of the tuberculosis is Class B or less.

4. The dosage of the arsenicals, when employed in combined syphilis and tuberculosis, should be reduced to one-half or one-third the usual dosage.

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A UNIFIED PLAN OF TUBERCULOSIS CONTROL[1]

BENJAMIN GOLDBERG

Legislation, founded on facts and science, is the basis for the unified plan of tuberculosis control as practised in the City of Chicago to-day.

Enabling Legislation: Legislation, as it affects a public-health campaign, is of two kinds,—enabling legislation and coercive legislation. Enabling legislation is, as the name implies, a legislation which enables us to bring the idea to realization. It is legislation which provides, in the first place and above all, the sinews of war or, in other words, the funds essential to the campaign.

The Glackin Act: This enabling legislation under which we operate in the City of Chicago, commonly termed the Glackin Act, gives to residents of cities or villages in the State of Illinois the right to determine by referendum vote the proposition as to whether they will levy a special tax to be used in the prevention and treatment of tuberculosis. In the City of Chicago, this tax rate is, at present, 1.2 mills on each dollar of valuation of real property and nets a revenue of over two million dollars a year.

Administration: The Act also provides that the mayor of the city or the president of the Board of Trustees of the village concerned, with the approval of the City Council or Board of Trustees, as the case may be, shall appoint a Board of Directors consisting of three members, one of whom shall be a member of the Board of Health. The power of these three directors, as regards administrative policies concerning tuberculosis work in the community, is practically unlimited. Every phase of such administrative work as it refers to tuberculosis, both in the sanatorium proper and in the field organization, is regulated by these three members.

This fact is a matter of first and greatest importance and deserves special emphasis at this point. It lays the foundation for the first essential of tuberculosis control, that is, centralized responsibility and unified administration.

[1] An address delivered at the annual meeting of the New York City Tuberculosis and Public Health Conference, November 22, 1928.

Our Problem in Chicago: The situation in Chicago calls for this type of unified administration, as it also does for that coercive legislation to be discussed later. In Chicago 7,798 new cases of tuberculosis were reported in 1927, and 2,567 individuals died of tuberculosis.

In a city like Chicago, with an estimated population of 3,155,600, rapidly growing and expanding, the problem might still be considered a fairly simple one if we were dealing with known quantities. However, the racial elements in our population have, in recent years, been undergoing great proportional variations, which variations have produced unknown quantities that are difficult of definite ascertainment. In the last ten years there has been an increase of over 125,000 Negroes, giving us for that group a total population of approximately 200,000 at this time. There is, in addition, a rapidly increasing colony of Mexican susceptibles who at present number approximately 8,500 in the city proper, and in greater Chicago perhaps 30,000. This latter Mexican population is also increasing by leaps and bounds.

Race Mortality: This unprecedented and startling increase in the susceptible elements of the population has changed the downward trend in our mortality tables. Comparing the mortality for the first nine months of 1927 and 1928, we find that there are 78 more Negro deaths from tuberculosis in 1928 than in the corresponding months of 1927. Sixteen more Mexican deaths from tuberculosis also occurred in the same period of 1928 in comparison to 1927. During the same interval of time there was for 1928 a total decrease of 25 tuberculosis deaths in the white race in this locality. It is seen, therefore, that, notwithstanding a reduction in tuberculosis mortality in the white race, there has been an increase in the general mortality of 71 from tuberculosis and this same relative increase is borne out in our statistics for the past five years.

An analysis of our general tuberculosis mortality for the year 1927 brings out in stark relief the enormity of the problem that this population of susceptibles is bringing to our community. If we subdivide our general tuberculosis mortality into Negroes, Mexicans and whites, we find that in 1927 we had 685 Negro deaths from tuberculosis from an estimated population of 170,481 Negroes, 68 Mexican deaths from an estimated population of 7,000 Mexicans and 1,798 white deaths from an estimated population of 2,978,119. To make the situation still clearer our statistics show that the tuberculosis death-rate for 1927 among the white race was 60.4 per 100,000, for the Negroes 402 per 100,000 and for the Mexicans 971 per 100,000. These figures indicate a ratio of 16

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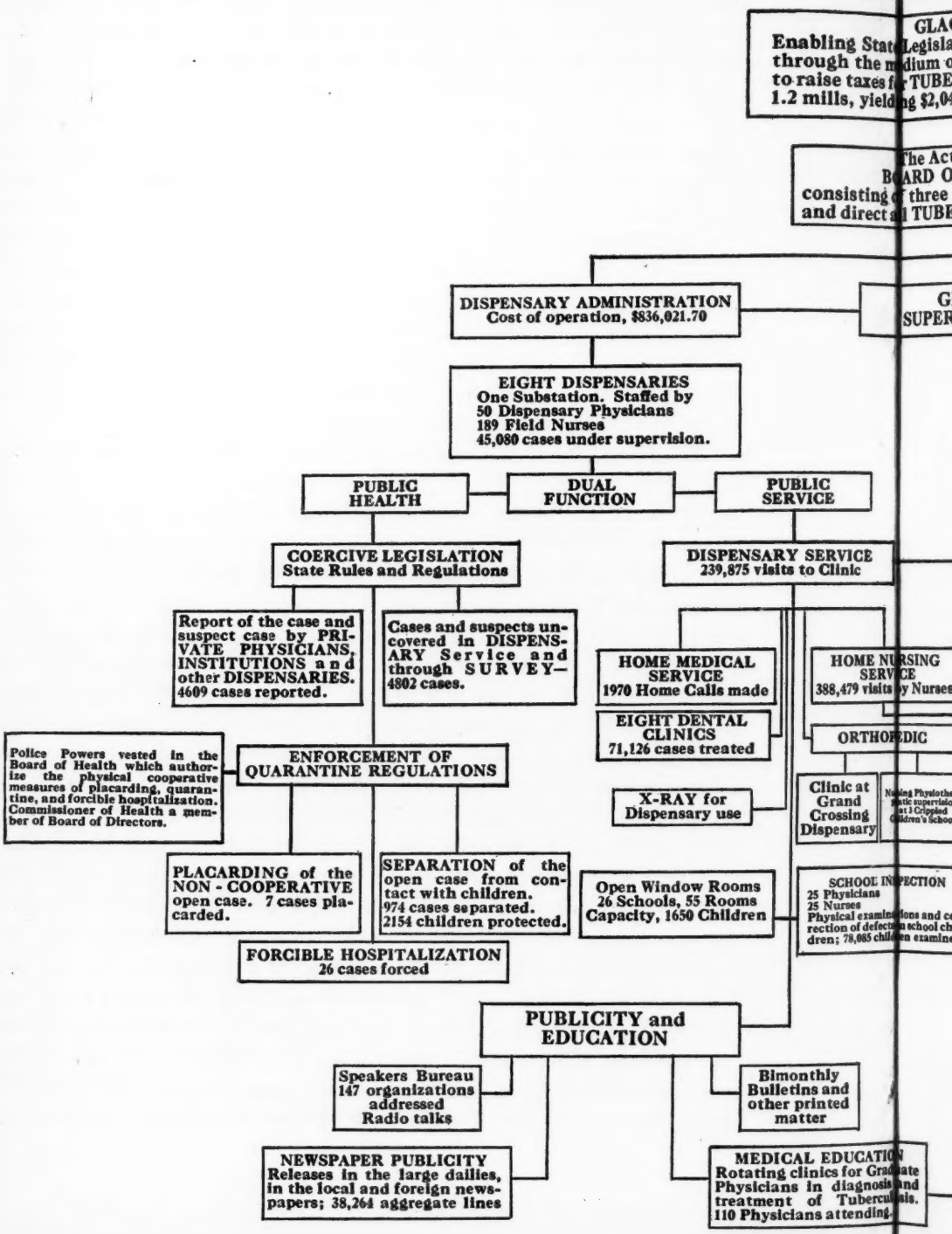
By BENJAMIN
Member and Secre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1.2 mills, yielding $2,04
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DISPENSARY ADMINISTRATION
Cost of operation, $836,021.70
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SUPER
EIGHT DISPENSARIES
One Substation. Staffed by
50 Dispensary Physicians
189 Field Nurses
45,080 cases under supervision.
PUBLIC HEALTH
DUAL FUNCTION
PUBLIC SERVICE
COERCIVE LEGISLATION
State Rules and Regulations
DISPENSARY SERVICE
239,875 visits to Clinic
Report of the case and suspect case by PRIVATE PHYSICIANS, INSTITUTIONS and other DISPENSARIES.
4609 cases reported.
Cases and suspects uncovered in DISPENSARY Service and through SURVEY—
4802 cases.
HOME MEDICAL SERVICE
1970 Home Calls made
HOME NURSING SERVICE
388,479 visits by Nurses
EIGHT DENTAL CLINICS
71,126 cases treated
ORTHOPEDIC
Police Powers vested in the Board of Health which authorize the physical cooperative measures of placarding, quarantine, and forcible hospitalization. Commissioner of Health a member of Board of Directors.
ENFORCEMENT OF QUARANTINE REGULATIONS
X-RAY for Dispensary use
Clinic at Grand Crossing Dispensary
PLACARDING of the NON - COOPERATIVE open case. 7 cases placarded.
SEPARATION of the open case from contact with children.
974 cases separated.
2154 children protected.
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Capacity, 1650 Children
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25 Nurses
FORCIBLE HOSPITALIZATION
26 cases forced
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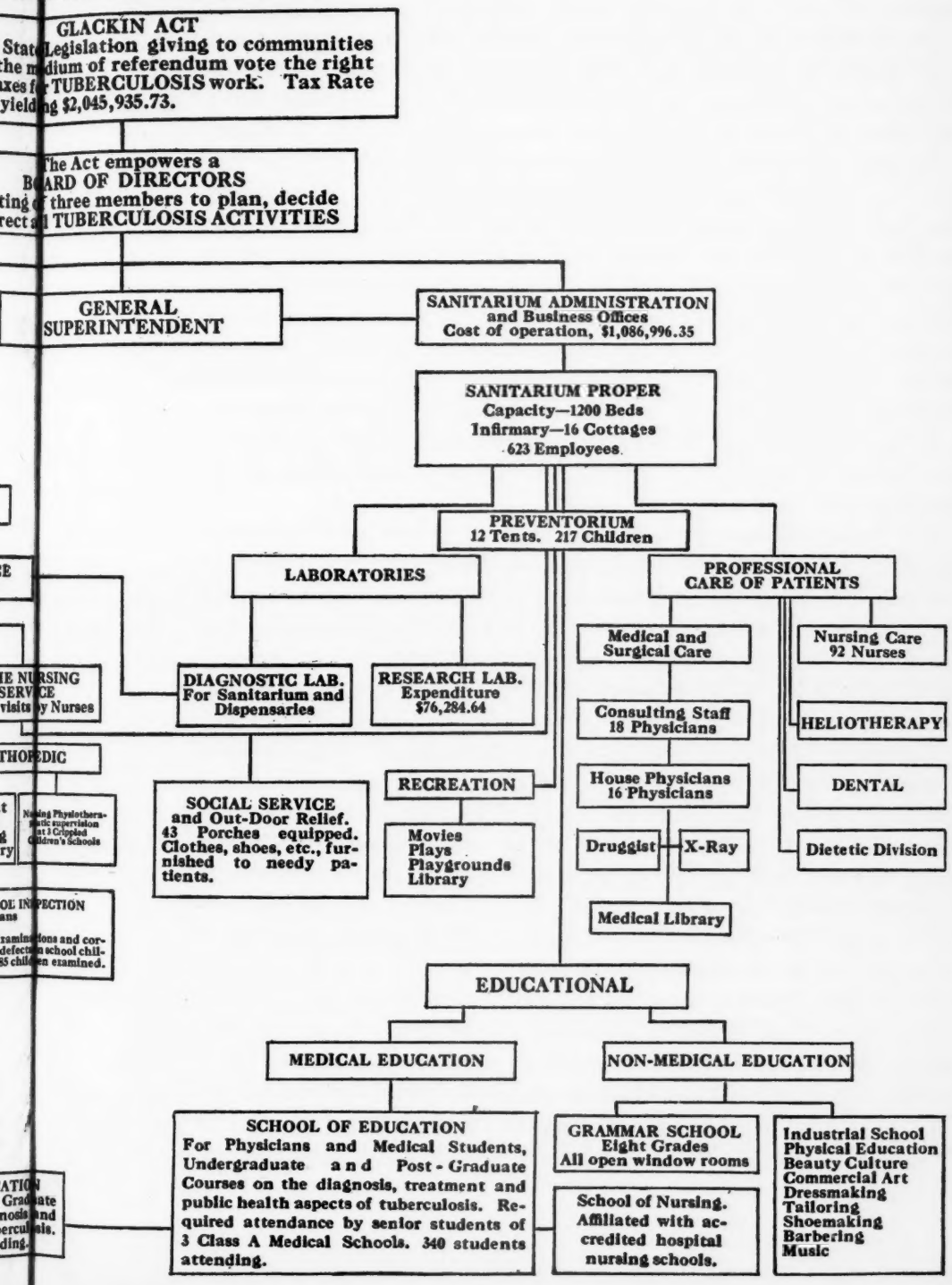
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SCHOOL OF EDUCATION For Physicians and Medical Students, Undergraduate and Post-Graduate Courses on the diagnosis, treatment and public health aspects of tuberculosis. Required attendance by senior students of 3 Class A Medical Schools. 340 students attending.
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School of Nursing. Affiliated with accredited hospital nursing schools.
Industrial School
Physical Education
Beauty Culture
Commercial Art
Dressmaking
Tailoring
Shoemaking
Barbering
Music

Mexican deaths to one white death and 6 Negro deaths to one white death.

The surface indications might tend to show that the apparatus and organization which had been developed to combat tuberculosis in resistant races was not adequate to meet the excessive demands of unrestricted migration of susceptible race units to a large urban centre. However, your speaker considers it safe to say that no conceivable organization, under present-day municipal complexities of life, could immediately effect a lowering of the total tuberculosis mortality in the face of this epochal increase in the migration of susceptibles uneducated as to individual health or public health. The conflagration will continue to burn as long as fresh oil is thrown upon the blaze. As long as individuals highly susceptible to tuberculosis are added by the thousands and even hundreds of thousands to our population, a tuberculosis organization must strain and creak and crackle in every joint to meet the onslaught.

It is, perhaps, this feature in the racial composition of our Chicago population which has, to some extent, urged upon us the detailed refinements in our program of unified control.

Coercive Legislation: The Glackin Act, as stated, is merely enabling legislation; it provides the finances which make possible the combat. In itself it is innocuous, pacifist, ineffective. It has nothing to do with health-enforcement measures; it has no grip, no teeth. To meet our problem in Chicago, or indeed in any other large American city, we must have, in addition to the primary enabling legislation, the power and authority of coercive legislation.

Some may object to this term "coercive legislation." We, however, must remember that we are dealing with a communicable disease and that the menace of this disease in the large cities, owing to factors already discussed, is on the increase. We should also remember that it is a disease transmitted by contact, especially by intimate family contact, and that if we are to prevent infection we must use all possible measures to break up this mode of transmission. We must use all measures of education, of persuasion, of humanitarian pleading. In addition, however, we should have in reserve the means or measures of protecting the community by force from the menace of the open case. We must extend one hand in a gesture of friendliness, of good cheer, of benediction to the careful and considerate consumptive, while the other hand behind our back holds the "big stick" for the careless and recalcitrant tuberculous individual. The "big stick" in this instance is coercive legislation.

State Rules and Regulations: Coercive legislation, as practised in Chicago, is dependent, for the greatest part, on the state rules and regulations as laid down by the Illinois Department of Public Health and fostered by our organization. The rules and regulations specify certain essential measures without which, according to our modern conceptions of epidemiology, any program aimed at the prevention of tuberculosis must fail. The reporting of the case, the home supervision of each patient, the special management of the open case, the matter of child contact, and segregation are dealt with specifically.

The Report: The compulsory report of the known or suspected case of tuberculosis is the first essential. Without this report the antituberculosis campaign in a community can have no life, no development, no growth. We cannot fight a menace which we can neither see nor feel. We cannot fight a menace over which an ignorant people or misguided physicians throw a mantle of invisibility. The problem must be dragged from the gloom of the cellar into the light of day. Tuberculosis supervision can only function when tuberculosis is located through the medium of the report.

We regret that the necessity for this first measure of control is not universally admitted. As yet in certain countries and communities it is not practised, and this fact makes all other procedures ineffective and barren and all financial expenditures in this work futile.

Our Hearing Board Experiment: In 1908 tuberculosis for the first time was made a reportable disease in Chicago. In this first year, 2,577 new cases were reported while 3,915 deaths from tuberculosis occurred. It is interesting to compare these figures with the figures for 1927, which show 7,798 new cases reported and 2,567 deaths. These figures indicate, if such indication be necessary, the truth of the axiom in tuberculosis work,—that as the number of cases located and placed under supervison increases, provided the supervision be adequate, so does the tuberculosis mortality decrease.

To ensure proper and thorough reporting of the cases a Hearing Board was established in 1918. Through it physicians who were lax in reporting these cases were called to account for their laxity. This Hearing Board served the purpose well in the early days; though it has been discontinued in recent years it may be at any time again called into function should the situation so demand.

Supervision: After the report defining the location of the patient the next step is supervision. Irrespective of the origin of the tuberculosis

report every patient, whether diagnosed by the private physician, the private clinic or hospital, or in our own system of dispensaries, immediately comes under the supervision of our organization.

We realize that the coöperation of the private physician is vital to a tuberculosis campaign and we are willing to make some sacrifice to gain this coöperation. We cannot, however, sacrifice to a serious degree the public-health prerogatives, which demand that all possible weirs and barriers be constructed to oppose the spread of tuberculous infection through the community. The medical management of the case by the practising physician is his responsibility. We insist, however, that the case be managed in such a way that it will offer as little menace as possible to community health.

It may be of interest to say a word or two concerning our procedure in the case of patients under the supervision of a private physician. As the first step an initial letter is immediately sent to the physician on receipt of the report. It may not be amiss to quote a paragraph of this letter:

It is essential from the viewpoint of public health and the welfare of the patient that he have certain information. We, therefore, earnestly recommend that you inform patient and family of the facts which are underscored in the enclosed copy of the regulations.

A copy of the *State Rules and Regulations for the Control of Tuberculosis* is sent with the letter.

Another paragraph of this letter states:

In compliance with these regulations and to insure proper supervision of the case, one of our nurses will visit the home of the patient at definite intervals.

The letter further emphasizes the fact that the nurse is not a police officer, but a graduate, registered nurse working for the welfare of the family and under the supervision of the practising physician, in so far as the medical treatment of the case is concerned.

If a patient under supervision of a private physician dies we send out our form letter no. 2. This letter draws the attention of the practising physician to the necessity of examining the contacts. A paragraph of this letter reads:

Of course, you realize that it is of the first importance to have the contacts, especially children contacts and young adults, examined for possible infection and disease.

For suspect cases reported by the private physician we have another form letter which, after a certain interval of time, requests that the physician diagnose the patient either as tuberculous or nontuberculous, in order that the case may be cleared. A paragraph of this letter reads:

> If the patient has left your supervision or is unable to pay for further medical attention, will you please advise us of this fact?

This paragraph takes care of the case of the wandering patient who will not give the private physician opportunity to clear up the diagnosis. We have the address from the physician's report and follow up the case.

The Nurse's Calls: The nurse makes an initial visit as is the order in the dispensary case. Furthermore, she continues to make visits at regular intervals, once a month or more frequently at the discretion of the physician in charge of the dispensary. During the first nine months of this year we had 6,231 private physicians' cases under supervision; during that time we estimate that our nurses made 37,386 visits on these cases.

Comparing this with our dispensary routine we find that we supervised 13,160 dispensary pulmonary cases during this time, with a total of 78,968 nurses' calls. It will be seen then that the private physicians' cases are called on almost, if not quite as frequently, as are the dispensary cases. In addition to the routine calls there are, of course, special calls for sputum specimens, for isolation, for breaking up of contact, etc.

Consultation, which we offer free of charge, is a feature of our dispensary service. The practising physician has available, at any and all times, the services of a specialist in tuberculosis for the purposes of consultation and advice. In addition the private physician is permitted to send in, for X-ray and fluoroscopic examinations, patients who cannot afford to pay for such services at a private laboratory. We have an excellent radiographer, and the physicians profess themselves very well pleased with this feature of the service.

In maintaining this supervision at the present time 189 graduate, registered nurses, assigned to field or home service, are employed. The city is divided into eight dispensary districts; each of these dispensary districts is, in turn, subdivided into 16 or more smaller districts, controlled by the individual field nurse. Our field nurses exercise a dual function. Primarily, as a public-health nurse, she is responsible for the maintenance of public-health standards. Secondarily, as a home-service nurse, she is responsible for nursing care and management in the

home. Serving the dispensary patient she is subject to the instructions of the dispensary physician; in the case of the private physician's patient she is, of course, subject entirely to the instructions of the private physician.

The Open Case: The open case is the alpha and omega, the beginning and the end, of a tuberculosis campaign. Any campaign that does not include efficient supervision and management of the open case is worse than useless. We know that tuberculosis is a communicable disease; we know, furthermore, that the medium of communication is the open case; we know that the open case is the sower of the seed, is the individual who broadcasts infection throughout the community; we know, or most of us nowadays think we know, that most of our tuberculosis is a childhood infection contracted from the open case in the early years of life.

We are convinced of all this and still many of us are unwilling to go the full length of our convictions. Most of us admit that the open case should be segregated; that is to say, should be segregated sufficiently to afford a sufficient degree of protection to susceptibles and to children. Most of us, however, are unwilling, as stated, to go the full length of our convictions. In Chicago we have, I think, since 1918 gone the full length of our convictions and applied every measure at our command to protect the community from the open case.

Child Contact: Child contact with the open case was our greatest problem. Rule V of the state regulations reads as follows and gives us the necessary coercive legislation in the matter:

> No child under the age of sixteen (16) years of age (*sic*) shall live in the same home, apartment or other place of abode or habitation occupied by a person suffering from active or open pulmonary tuberculosis (consumption).

Your speaker, as chairman of a committee, in 1918 wrote into the state regulations the above paragraph. Furthermore, he went out on the streets to enforce the provisions of that paragraph when it was a pioneer proposition and education had not as yet erased public opposition. Injunction proceedings fought in courts quickly established legal precedents for the procedure.

At the present time this provision of the state law is enforced to the letter. No child under sixteen years of age remains in contact with an open case *if we have knowledge of the condition, that is, if the case has been reported.* There were on November 1st, in Chicago, 3,199 open cases. Of these only 24 were in contact with children. All of these 24 cases

were in the process of clearance, a ten-day clearance interval after the report of the positive sputum being allowed.

At the present time this procedure is not as arduous as it was during the early days of enforcement. It may not be amiss to state, at this time, that in the early days the ambulance crew responsible for forcible hospitalization invariably went armed.

Friendly Adjustment: In each case we, of course, first attempt friendly adjustment. This method has proved effective in 95 per cent of the cases. In the case of the private physician's patient we find that when our nurse calls the patient is advised already as to the necessity of removing the children. In fact, the children, on the advice of the physician, are often removed before the nurse makes her first call. In the case of the dispensary patient the parents are advised concerning the great danger to the children. The situation is explained clearly and emphatically.

Any one of three courses is open to the family:

1: The patient may go to a sanatorium
2: The patient may find a home where there are no children
3: The children may be removed either to our preventorium, to the home of relatives or to some other home or institution in which they may not be submitted to continued, massive infection.

The Noncoöperative Case: A patient is never considered noncoöperative until the field nurse, supervising nurse and chief dispensary physician have, in turn, visited the patient and have failed to secure the adjustment. If the case is finally considered noncoöperative this organization reports the patient to the Commissioner of Health, who furnishes the police power necessary for the enforcement of our three routine methods of coercion and automatically orders that action be taken. These measures are (1) forcible hospitalization, (2) the placard and (3) the quarantine officer's call.

Forcible hospitalization: It is only in exceedingly rare instances that it is necessary to employ forcible hospitalization. An ambulance is sent to the home of the patient and he is removed, by force if necessary, to the Cook County Hospital. In a carefully guarded ward in this institution he remains, willingly or unwillingly, until such time as home arrangements, in compliance with the law, are made.

Forcible hospitalization in Chicago is not a gesture. It is a fact. The isolation of the open case, sufficient to protect the child, is enforced

to the letter. In 1927, 2,154 children were separated from contact. As already seen, on November 1, 1928, we had 3,199 open cases, and of these only 24 were in contact. These figures speak for themselves. They will indicate the effectiveness and thoroughness of the work. More important still, the spirit of understanding and coöperation daily is becoming more evident, notwithstanding the large number of cases in which contact was broken; notwithstanding the children removed from contact, it was necessary to resort to forcible hospitalization in only 23 cases in 1927.

The Placard: As less severe measures of coercive legislation, the placard and the quarantine officer's call are employed as the occasion demands. These measures are used for cases which are not open or which, if open, are not in contact with children and are designed to correct less serious infractions of the health law.

The Sanitarium: The Sanitarium and field departments are linked together intimately through the medium of the supervision exercised on the individual patient both prior to his admission to the Sanitarium and following his discharge. The patient, before his admission, is examined by the dispensary physician, classified according to his physical condition, and admitted to the Sanitarium as soon as a vacancy arises in his classification.

A word concerning the Sanitarium proper: At the present time our sanatorium, the City of Chicago Municipal Tuberculosis Sanitarium, has a capacity of 1200 beds, of which 750 are in the infirmary or hospital division. There are approximately 1300 more beds for tuberculous individuals in Cook County, distributed between the Cook County Hospital, Oak Forest Tuberculosis Hospital, and several private sanatoria. The Sanitarium is free to all, irrespective of race, color, creed or economic condition. The rich are eligible as well as the poor. Our Sanitarium has more than justified its existence. It has achieved a reputation in the community which is felt everywhere and which has created a long waiting-list of almost 700. Patients, even well-to-do, seem to prefer to come to this public institution rather than go to a private sanatorium. Our waiting-list in the last year has lengthened greatly, notwithstanding the fact that our patient turn-over has increased to the extent of 900 patients a year.

In 1926 the average length of stay at the Sanitarium was over eleven months. At the present time it is approximately six months. Instead of approximately 1200 patients cared for at the Sanitarium in 1926,

during the year 1928 present conditions indicate that we will have cared for 2100 patients.

In the past, only too frequently, a tuberculosis sanatorium has been one of two things. It has, on the one hand, been a small, private institution, supervised by a medical staff with limited potentialities, which cared for early cases, many or most of whom were curable. On the other hand, it may have been a large municipal institution, utilized predominately as a dumping-ground for hopeless cases whose only reason for sanatorium residence lay in the fact that they constituted a menace to the community.

There has been one feature lacking in the institutional treatment of tuberculosis, and it is this feature, particularly, which I wish to emphasize. Your speaker, in five years of resident sanatorium work, supplemented by many years of consultation work, had observed that nontuberculous or tuberculous complications, in the case of the tuberculous, did not meet with the best measures in diagnosis or treatment. The advantages of the specialistic groups of physicians available to patients in general hospitals were not available to patients in tuberculosis institutions. Frequently progress toward recovery was impeded or retarded owing to the fact that the secondary manifestations of tuberculosis or complicating conditions did not receive proper attention.

Sanatoria, at least those adjoining large cities, should have, to some degree, the benefit of specialists' services. Our large cities, with their medical schools and highly specialized medical profession, should be able to furnish such services and skill to sanatoria in their environs.

In Chicago it was felt that this could be done, and a group of men, chosen from the professorial ranks of our leading universities, were selected to constitute an attending and consulting staff. This staff, it was decided from the first, should visit the Sanitarium at regular intervals and should work in close coöperation with the resident staff of the institution.

Team-work was the keynote. The resident staff was interested and stimulated, the consulting staff was pleased with the material and equipment supplied, and, in a short time, what previously had been just a sanatorium, in the usual sense, became a highly specialized, general hospital. As stated, the material, equipment and opportunities, unsurpassed in any one private hospital in our city or in any tuberculosis institution in any city, kept the interest of the professional staff keyed to a high pitch; on the other hand, the patients received a service not

available in other institutions and have consistently evinced their appreciation by better coöperation and a more optimistic outlook.

Research: Our research program is showing promise of great development. The consulting specialists, whose trained powers have never before been devoted to tuberculosis, are gleaning new information on what is, to them, virgin soil. This clinical research by specialists of training and ability should be a valuable supplement to the vast amount of research constantly taking place in our research and laboratory division.

Diet: A word about diet. We have taken the subject of diet both in the home and in the Sanitarium rather seriously. We have introduced a new system of dietetic supervision and control, described in detail in our May–June, 1928, *Bulletin*. Our experiment in the matter of diet possesses some pioneer features and has met with considerable success. It has been instrumental in removing one of the most serious criticisms of institutional service, that is, unduly standardized and monotonous diet.

Education: Education furnishes another example of the close correlation and coördination of the activities of both the dispensary and Sanitarium branches. Heretofore, the tuberculosis campaign has been largely waged with the idea of educating the lay individual to the dangers of the disease and to its modes of prevention. Your speaker, for many years, has felt that it is useless to teach the lay individual to suspect tuberculosis unless the practitioner of medicine has learned to confirm or remove that suspicion.

This thought of medical education for the physician was one of the ideas kept in mind when our consulting staff was appointed. One of the purposes in the appointment of the highly specialized attending staff at the Sanitarium was the establishment of a faculty for a school of tuberculosis, in which every specialist would teach that phase of tuberculosis which concerned his special work. While there were some who doubted the feasibility of this plan, a curriculum was nevertheless arranged and the program started. During the first year approximately 340 students, representing three of the class-A medical schools of Chicago, attended these courses of instruction, arranged in the form of both resident clerkships and special lectures. The students were enthusiastic concerning the work received, and demands for the course at the Sanitarium became so great at the respective schools that our curriculum, after the first year, became "required" in these class-A medical schools.

We also created a program of education for the general practitioner, busily engaged in daily routine and, consequently, unable to attend postgraduate courses. We planned to take the teaching resources of the Sanitarium and dispensary organization into the different communities, to the very doorstep, as it were, of the practising physician. We gave the local physician courses, both didactic and practical, in the various phases of tuberculosis work. In addition, the physicians received personally supervised and practically individual instruction in the diagnosis of chest conditions in our dispensaries.

Our first experiment in this course of instruction to the practising physician was conducted on the South Side, in the Negro district. Over fifty Negro physicians attended the first series of lectures and courses of practical instruction. At the conclusion of the course certificates were presented to the physicians who had attended the course. At this ceremonial, in a large open meeting attended by over one thousand persons, the statement was made by the president of the National Medical Association, which is the Negro organization throughout this country, that this was the first time that a postgraduate course had been brought to the Negro in this country. The physicians expressed keen appreciation, and we expect this appreciation, their increased interest in their work, and their increased skill in diagnosis to be valuable factors in promoting the welfare of our antituberculosis campaign.

In the colored districts we are following this course of practical instruction among the physicians with an intensive house-to-house survey of the poorer districts in which these physicians practice. You can readily see the hook-up. The survey is being made by our nurses, who will refer patients, when economically possible, to these practising physicians whose interest in the subject of tuberculosis is already stimulated.

This plan of education for the practising physician, having met with a great measure of appreciation and success, still continues in effect. We propose to swing from one district to another, and from one dispensary to another, carrying this rotating clinic to the physician who is not at leisure to come to us. Past and present indications foreshadow great things for the future of our rotating clinic.

In concluding, your speaker wishes to emphasize the fact that in a brief period it is only possible to sketch roughly the main features of a tuberculosis campaign in a large, metropolitan city of present-day America. I have tried to bring out the fact that in Chicago we have

operative a unified plan of tuberculosis control, that we have coördinated and correlated the functional activities of all branches of the institution in so far as it is humanly possible, that the Sanitarium proper, the dispensary organization and the laboratory organization coöperate and act as a unit under the direction of the Board of Directors, that the compulsory reporting of the known or suspected case of tuberculosis is the first step in any antituberculosis campaign, and that the proper supervision and management of the open case demands certain coercive measures which may be deemed drastic but which are nevertheless vital.

It may seem that the speaker has unduly stressed the field or dispensary activities. He has, however, always been impressed with the undue importance attached to the sanatorium. He feels that the sanatorium is the battle-ground of the individual, where the patient may fight his battle to an issue, successful or unsuccessful, or where, at least, he may learn the rudiments of a warfare that is to continue outside sanatorium walls. "The Field" is the great battle-field of the public, the Armageddon on which the decisive battle must be fought, in which all physicians, public-health workers, social-service agencies, charitable agencies, etc., should join hands against the common enemy and avail themselves of every weapon of preventive medicine, to conquer and root out tuberculosis from the community.

OBLITERATIVE CHANGES OF THE PULMONARY LYMPH-VESSELS IN TUBERCULOSIS[1]

J. DWIGHT DAVIS[2]

In the pathogenesis of pulmonary tuberculosis the lymphatics are recognized as one of the most important pathways in the spread of the infection. Even with this recognition, however, the literature contains but few facts concerning the exact status of the lymph-channels themselves. This is largely due, it would seem, to the fact that these channels, although acting as an agent in the spread of the infection, usually remain healthy. The present study was attempted to determine whether any pathological changes could be recognized in the lymph-vessels in those infections in which the latter were acting as the secondary pathway between the primary pulmonary focus and the secondarily involved bronchopulmonary lymph nodes, and also whether lymphatic involvement could be found extending from other pulmonary tuberculous foci.

That the lymph-vessels act as a secondary pathway in the spread of tuberculosis was first definitely expressed by Cohnheim. As Cohnheim's law it is stated that tubercle bacilli reveal the site of entry into the body by setting up characteristic changes in the lymph nodes which receive the lymphatics from the area where the bacilli first enter. However, in 1876, Parrot recognized that the primary respiratory focus was within the lung and that the bronchial lymph nodes were involved secondarily to the focus in the lung. He expressed this idea as "*La loi les adenopathies similaires*," or the law of similar adenopathy. In 1898, Küss, a pupil of Parrot, corroborated this statement and, in addition, asserted that the lymph-channel between the primary pulmonary focus and the secondarily involved lymph node remained healthy.

Between the time of Parrot and the year 1912 these observations were further corroborated by such authors as Hutinel, Hervouet, Winkler, E. Albrecht, and H. Albrecht. In all their reports comparatively few

[1] Abridgment of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

[2] Work done in the Section on Pathologic Anatomy, The Mayo Clinic, Rochester, Minnesota.

cases were recorded in which the bronchial or lymph nodes of the hilum presented evidence of tuberculosis without revealing a primary focus within the lung. But it was not until 1912, when Ghon first published his work, that the primary pulmonary phase was generally recognized. Aschoff soon afterward began his survey and gave a classic lecture, reviewing the work of others and adding his almost incontestable view that the primary infection arises from a pulmonary source.

Delafield and Prudden stated that tuberculous lymphangitis occurs in both large and small lymph-vessels. They recognized two types, namely, a formation of miliary tubercles, and one of diffuse tissue. The latter forms in the wall and projects into the lumen, and in the smaller vessels it may completely fill the lumen. As Karsner stated, lymph-vessels offer a favorable site for the growth of tubercles; tuberculous involvement of them is, therefore, extremely common. It may occur as miliary tubercles within the wall of the lymphatic vessel, or it may occupy both lumen and wall, converting the lymphatic vessel into a more or less caseous nodular mass. The latter process, he explained, is seen in perivascular and peribronchial tuberculosis of the lungs; the former is most common in tuberculous involvement of the lymphatics of the intestine and mesentery.

Warthin claimed that secondary tuberculosis of the lymph-vessels, particularly those of the mesentery and intestine, is common. Miliary tubercles may be found in the walls of lymph-vessels leading from the part; or the vessel may be diffusely enlarged, appearing as a cord-like structure. In pulmonary tuberculosis, extension is partially through the agency of the pleural, interlobular, and peribronchial lymphatics. The infection spreads along these channels, often giving rise to beaded rows of miliary tubercles along their course.

The lymph-vessels of the intestine and mesentery are accredited as those which are most commonly involved in tuberculous conditions. Lejars, in 1891, writing on tuberculous lymphangitis, stated that tuberculosis of the lymph-vessels was first observed in the intestines by Andral, who described lines like strings of beads along the mesentery originating from intestinal ulcers. Thaon, in writing on tuberculosis of the lymphatics, stated that in tuberculosis of the intestines, when the ulceration reached a certain depth, nothing was more common than to see the lymphatics knotted, interlaced and bleached, forming a network in the visceral peritoneum corresponding to the ulceration.

Tuberculous lymphangitis of the intestines and mesentery has been

recognized as one of the most common forms of tuberculous involvement of the lymph-vessels, but that of the superficial vessels of the extremities is not as common. Lejars, in 1891, and Jordan, in 1898, reviewed the literature on this superficial form of lymphangitis and described the condition well. Lejars stated that in 1870 Bazin observed the first typical case of tuberculous lymphangitis of the arm. He described the lymphangitis as being characterized by rosary-like rows of nodules with connecting tracts of vessels.

A rare type of tuberculous involvement of the lymphatic system is that of the thoracic duct. Comparatively few cases have been reported in which definite involvement has been found. The earliest case found in the literature is that of Andral who in 1824, after dissection of the thoracic duct in 300 cases, found pathological lesions in but five.

Whitla, in 1885, reported a case of general miliary tuberculosis in which he made the postmortem examination. The thoracic duct in its upper half was an impervious cord, the remains of the lumen of which, on microscopic examination, appeared only in the form of a transverse mark. Around this were seen only the firm fibrous thickened walls. Throughout the entire duct minute miliary tubercles were found.

Cornil and Ranvier have described the development of tuberculosis within the lymph-vessels. In the first stage, the lumina become filled with white globules and with cells of various forms proceeding from the vascular endothelium; the walls and the adjoining connective tissue are to a great extent filled with embryonic cells. In the second stage, the cells collected in the walls of the lymphatics and in the connective tissue form, with the cellular contents of the vessels, a nodule which has all the characteristics of tuberculous granulations. These nodules, placed in the track of the lymphatics, are at variable distances from one another, and have been in many cases confounded with granulations arising from the connective tissue. Thaon, in discussion, added that nearly all this work of proliferation is done at the expense of the lymphatic endothelium, and that the result is a caseous endolymphangitis mixed with granulations.

The walls of the earliest lymphatic capillary consist only of a single layer of endothelial cells. It is seen surrounded, however, by a fine layer of fibroelastic-tissue fibres, which act as an adventitial sheath. The lymphatics remain this way until they have reached a diameter of about 0.5 mm., when the wall forms into three layers. They closely resemble small veins, and, according to Jordan, except for the fact that they

contain lymph instead of blood it would be difficult to distinguish between them.

The three coats of which the walls of the lymph-vessels are composed are as follows: an intimal layer, having a single layer of flattened endothelial cells with a delicate subintimal fibroelastic-tissue membrane; a mesial layer, which also is thin, composed of fine, circular, smooth muscle fibres; and an adventitial layer, which is the heaviest, composed primarily of fibroelastic tissue, with comparatively few bundles of smooth muscle fibres, in longitudinal arrangement.

Nontuberculous thrombosis of the lymph-vessels, which is relatively infrequent, has been described by Opie. He stated:

> Thrombi may form in the lymph-vessels by the coagulation of the lymph or by deposition of fibrin on the walls of the vessels at the seat of degeneration or inflammation. These lymph thrombi are formed largely of fibrin and leucocytes and may detach and form emboli. The formation of the thrombus occurs under conditions which are dependent on the peculiar constitution of the lymph. The penetration of thrombokinase may bring this about. This condition is fulfilled whenever cells in contact with the lymph stream undergo necrosis.

This type of thrombosis is relatively infrequent, but was found by me in the case of

> a man aged thirty-nine years, whose history was that of influenza of three weeks' duration, with a protracted convalescence. At necropsy, the right pleural cavity contained 500 cc. of cloudy fluid, and the left 750 cc. A heavy fibrinous exudate was found over both lower lobes. The lower lobe of the right lung appeared dark red; crepitation was absent, and it felt extremely firm and heavy. Several small areas of infarction were found in the lower lobe. Also on the diaphragmatic surface of this lobe, yellowish-white, elevated, cord-like structures were seen in an area about 6 cm. in diameter. They were found in irregular, polygonal or squared arrangement. The arrangement and situation would indicate that they were the pleural lymph-vessels. Beyond this area, over the entire surface of the lower lobe, dilated, translucent grayish-white channels, disposed in the same arrangement, were seen. On sectioning, the lumina of the lymph-vessels of this area were seen to be filled with a yellowish-white substance, which held tenaciously to the walls. Deeper sectioning also revealed, chiefly within the interlobular septum, the same dilated vessels with their lumina also filled. On microscopic examination the typical form of a septic thrombus was seen. There was marked dilatation of the vessel, and its lumen was completely filled by a thrombus which was adher-

ent to the wall but which, during hardening, evidently had contracted and had torn loose in some areas (figure 1). The wall was slightly thickened, and surrounding the vessel was a loose connective-tissue reticulum, infiltrated with polymorphonuclear leucocytes, and a few mononuclear cells. The thrombus was seen to be composed chiefly of polymorphonuclear leucocytes, but there were a few large rounded mononuclear cells and small mononuclear lymphocytes. Interlacing the whole structure were fine tendrils of fibrin.

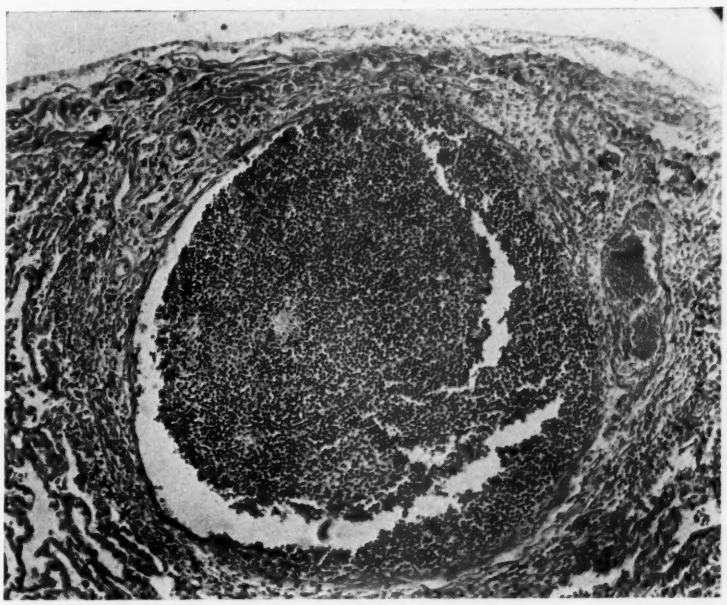

FIG. 1. A widely dilated lymphatic vessel filled with a thrombus which is composed chiefly of polymorphonuclear leucocytes and fibrin. Surrounding the lymphatic is loose connective tissue infiltrated with polymorphonuclear cells. Specimen from the pleural surface of a congested lung with multiple infarcts (× 60).

The thrombus of the lymph-vessels in this instance substantiates the theory of Opie. The close proximity of necrotic tissue to the vessels has resulted in the absorption of thrombokinase, and, at the seat of the degenerative process, a deposition of fibrin has occurred, filling the lumen and enmeshing the cells which are found as the constituents of the lymph.

In tuberculosis, also, the evidence of a formation of thrombi is found. One of the earliest reports was written by Klob who, in 1866, described a case of thrombosis in the lymph-vessels of both lungs.

In the course of routine studies of lungs of persons who had died from

various causes, I have found two examples of tuberculous thrombosis of lymph-channels. One was in the lateral portion of the left upper lobe in which, in a lung otherwise normal, a large caseating subpleural tubercle was noted.

Two grayish-white, enlarged, elevated, firm vessels radiated from this tubercle beneath the pleura in the direction of the hilum, and extended over a distance of nearly 2 cm. Beyond this point the vessels continued as dilated, clear channels, and for a distance of several centimetres surrounding the tubercle they

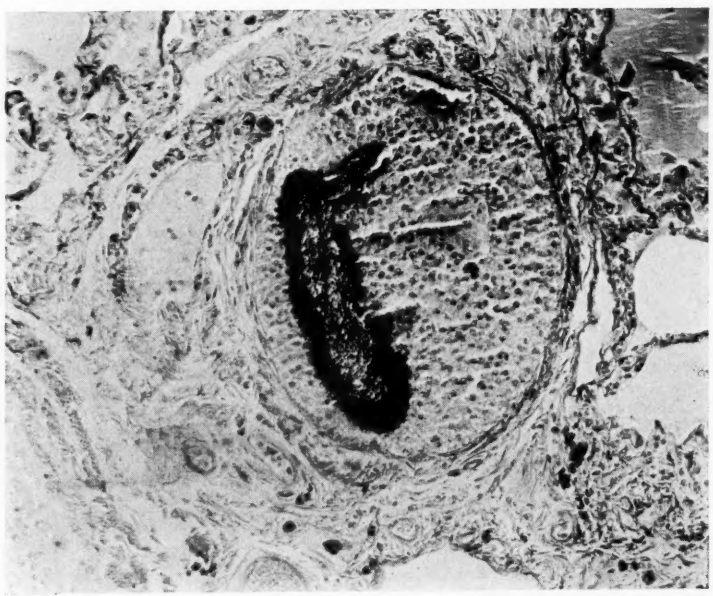

FIG. 2. A dilated and thrombotic lymphatic extending from a tubercle on the pleural surface. The lumen is partially patent and has been filled with carmine injected into adjacent dilated lymphatics (× 60).

were dilated and transparent. These vessels were in irregular, polygonal forms definitely following the interlobular connective-tissue septum, a characteristic which is typical of the pleural lymphatics. An attempt was made to determine whether the grayish portion of these lymph-vessels was patent, and a 1 per cent aqueous solution of carmine was injected into the dilated transparent portion, a short distance away. The dilated portions of the vessels filled rapidly, bringing out clearly the pattern of the network which the pleural or superficial lymph-channels assume; but grossly there was no evidence of any carmine entering the grayish heavy portion. However, microscopic sec-

tions were made, and these portions of the lymphatics were seen to have small lumina which were filled with the granules of carmine (figure 2). The lymph-vessels appeared almost occluded by a thrombus. This thrombus was composed chiefly of cells which were slightly ovoid, with irregular, rounded, somewhat granular nuclei. A few lymphocytes and polymorphonuclear cells were present. Practically no fibrin could be seen. The walls of these vessels were but slightly thickened and but little reticulum or connective tissue was seen surrounding them. Lymphocytes were not found in the wall.

The second example of tuberculous thrombosis was found in the lung in a case in which there had been no history of tuberculosis and a diagnosis of tuberculosis had not been made. The lungs were removed at necropsy and inflated, and a roentgenograph made.

In the right lung was a large subpleural tubercle on the lateral margin of the upper lobe, which I considered the primary focus. Examination of the apex revealed an area of puckered scarring with signs of infiltration, indicating a chronically active tuberculous focus. This was proved by microscopic examination to be active. Extending from the area of apical scarring and into the hilum, a linear shadow was noted in the roentgenograph. This area of streaking was followed through its entire length by microscopic sections. It was found to be a lymph-vessel, one of the deep set associated with the pulmonary artery and lying between the artery and bronchus. There was a fairly dense fibrous proliferation surrounding this vessel, probably an increase of the adventitial sheath. The lumen was filled by a thrombus throughout its course. The thrombus was seen to be composed principally of ovoid cells quite densely packed, with irregular, rounded nuclei which stained fairly deeply and were somewhat granular. Some evidence of fine fibrin interlacing these cells was also seen. Along the course of this lymph-vessel were tubercles which filled the lumen.

Tubercles within a lymph-vessel indicate that the thrombotic condition was tuberculous. In the first lung described the thrombotic area was immediately adjacent to a tubercle; this would exclude any process other than tuberculosis. In both of these instances of thrombosis of tuberculous origin, marked differences were noted between them and the septic or nonspecific type which previously was presented. The greatest variation is in the type of cell composing the thrombus. The cells found chiefly in the septic thrombus are those which are ordinarily found as the constituents of the lymph; namely, polymorphonuclear leucocytes, and large and small mononuclear cells of the lymphocytic type. The cells found chiefly in the thrombus of tuberculous origin

are primarily of rounded or ovoid type, and they contain a rounded, slightly granular nucleus. Another variation which is extremely important is the absence of the endothelial lining of the wall of the lymph-vessel which contains the thrombus of tuberculous origin. Also, there is no infiltration in the wall or surrounding tissue of the tuberculous vessels, except where tubercles occur; and where infiltration does occur it is of a lymphocytic type, rather than of the polymorphonuclear type which is found in the nonspecific type.

The cell found in the tuberculous thrombus probably has been derived from the endothelial lining of the lumen of the lymph-vessel. Foot has shown in experimental work that, following inoculation with tubercle bacilli, this type of cell, which he calls a fibroblast, may originate from the endothelium of the vascular system. The proliferation of the endothelial lining of the lymph-vessels and the transformation of its cells into fibroblasts in tuberculous conditions, are due, I believe, to a specific sensitivity to tuberculous products which the endothelium acquires. That such sensitivity occurs has been shown experimentally by Petersen and his coworkers. Their study was on the alteration of the thoracic lymph, using normal and tuberculous dogs, and injecting tuberculin.

Eberson, in discussing the significance of lymphangitis with tuberculin reactions, stated,

> The lymphatics are the distributors of tuberculosis, and the phenomenon of lymphangitis speaks for an active tuberculous process. A glandular reaction following an injection of tuberculin is akin to a more pronounced skin reaction, and is in turn an integral part of the most pronounced reaction, lymphangitis, which results from an active sensitization of the lymph channels to the product of the tubercle bacilli.

Herring and MacNaughton also have noted a special sensitiveness of the lymphatic system to tuberculosis. This was found by them chiefly in the lymph nodes and took the form of a lymphocytosis. They observed that, when one node of a lymphatic chain is affected, and before any sign of general tuberculosis appears, a lymphocytosis is discoverable in the next nodes in this chain; but in these nodes they have never been able to demonstrate the presence of tubercle bacilli. They believe that the lymphocytosis is due to the toxins produced by the bacilli, or to toxins resulting from the action of the bacilli on tissue. They also noted that this reaction occurs first only in those nodes which are in the lymphatic chain which drains the affected area.

Baumgarten, in 1882, wrote on the proliferation of the endothelium of the lymph-vessels of the wall of the intestine and on the transformation of its cells into other forms. He stated that the ordinary endothelial cells of the lymph-vessels become transformed into large round or cubical, or short or polyhedral structures. In the more advanced stages the lumina are often dilated, and are filled with two or more layers of cells. Baumgarten, however, did not attribute this transformation of endothelium to the action of a specific disease. He claimed that it could occur in inflammatory processes involving the intestinal mucous membrane, such as catarrhal, croupous, diphtheritic, typhoid or tuberculous enteritis, or in inflammations beginning in the serosa of the intestine. He further stated that the change in the endothelium may take place without the surrounding tissue showing signs of inflammation.

In my work I recognized that a thrombus occasionally is found in the lymph-vessels leading from a tuberculous area of the lung, and I assumed that this thrombotic process originated from a proliferation of the endothelium which forms the lining of these vessels. I then attempted to determine whether there were any other changes involved. A series of 124 lungs was studied in the Section on Pathologic Anatomy of The Mayo Clinic. Ninety-two of these lungs were inflated and roentgenographed. With the aid of the roentgenograph, careful search was instituted for involvement of lymphatics leading from tuberculous foci. Examination was made of superficial groups of lymphatics and with the aid of cut-sections of deep groups. In most cases, however, no trace of involvement could be found in any of the lymphatic pathways of the superficial or deep groups. In three of the lungs so examined definite lymphatic involvement was found, and since this series was completed another case of the same condition has been discovered. One of the lungs presented two areas of lymphatic involvement, one in the upper and the other in the lower lobe. These will be described separately.

The first case in this series was found to be that of a man aged fifty years. The cause of death was determined as hypertension, with hypertrophy of the heart, and chronic diffuse nephritis. No history of tuberculosis was recorded.

On the right lung was noted an area of irregularly shaped apical scarring, measuring about 2.5 by 1.7 cm. in the widest diameters. Below the apex, on the lateral surface, a subpleural calcified tubercle was found; and several smaller, grayish-appearing nodules were seen on the surface of the lower lobe. At the hilum one node was found which contained an area of calcification.

In the right lung, a vessel was seen running directly across the area of apical scarring with two branches leading toward the hilum. Later these branches united and continued directly into the region of the hilum, where they were lost. The appearance of the vessel was grayish-white, rounded and elevated above the pleural surface. It felt firm but not nodular. The situation and course suggested nothing else than lymph-vessels of the superficial set (figure 3).

In studying this lymph-vessel, evidently pathological and of tuberculous

FIG. 3. Drawing of a specimen of lung showing apical scarring with elevated and proliferated lymph-vessels over this scar and coursing to the hilum.

origin, sections were made through various portions. All presented the same microscopic picture. The vessel was found just beneath the pleura. It was markedly dilated, and the lumen was completely obliterated by a mass of cells which had no regularity of arrangement. The wall of the vessel was somewhat thickened, due to proliferation of the circularly arranged fibrous tissue. It appeared contiguous with the fibrous tissue of the pleura. Surrounding the lymph-vessel, in several places, was seen a moderate anthracotic deposit.

However, infiltration of the tissues by any type of cell could not be seen. The endothelial lining of the vessel had disappeared (figure 4).

The cells filling the lumen were compact, with their outlines, for the greater part, not distinguishable; but the outline occasionally was seen, and then it appeared roughly ovoid. The nuclei were of fairly large size, irregular, and chiefly ovoid, but occasionally rounded. They stained deeply, and their appearance suggested that they were granular in structure. Resemblance was immediately noted to the cell which composed the tuberculous thrombus. With the disappearance of the endothelium, which I considered had prolifer-

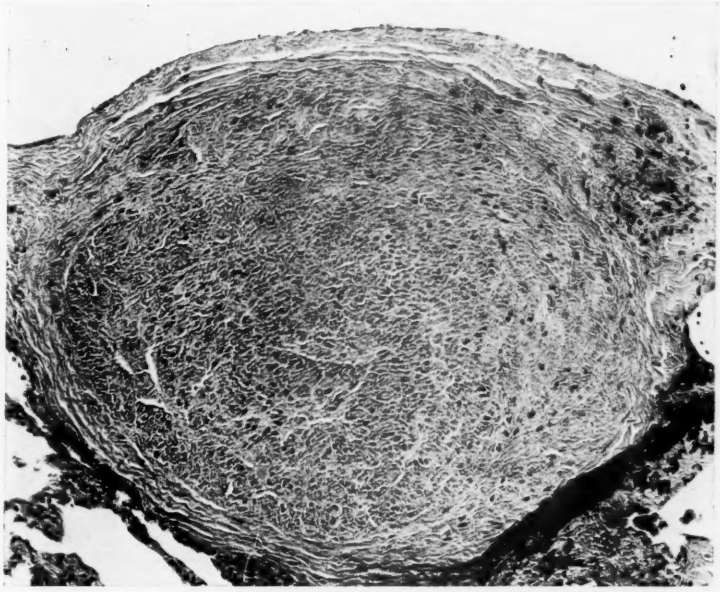

FIG. 4. Cross-section of the lymph-vessel, revealing dilatation and occlusion of the lumen by proliferated tissue. The wall is thickened by an increase of fibrous tissue (× 60).

ated into this mass of cells, I felt no hesitancy in calling them fibroblasts. Weigert's elastic-fibre tissue stain revealed but little of this type of tissue present at any point along the course of this lymph-vessel.

Also in the right lung in this case but on the mediastinal surface of the lower lobe, there was found a vessel extending from the margin of the lung through an area of dense anthracotic lymphoid tissue to the hilum. It could be traced to the node of the hilum which contained the evident calcified tubercle. The vessel appeared as a grayish-white, rounded, cord-like structure elevated slightly above the pleural surface of the lung. A study of this vessel was made by numerous microscopic sections taken along its entire course.

A section taken through the lymphoid tissue revealed that this structure contained an extensive anthracotic deposit. Immediately under the serosa of the pleura there was an enlarged lymph-channel which was completely occluded, and in the lymphoid tissue were four small tubercles, marked by a characteristic mononuclear proliferation.

On further study of the lymph-vessel the wall was found to be increased by evident proliferation of circularly arranged connective tissue. The endothelium lining the wall had disappeared. The lumen, except for a slit, which in the sections appeared narrow and irregularly transverse, was occluded by cells which were identical with those found occluding the lymph-vessel that extended from the apical scar. The cells appeared to be densely packed. The transverse slit, evidently the remnant of the lumen, had no lining of cells. Immediately surrounding the slit was a small zone of fibroelastic tissue, and

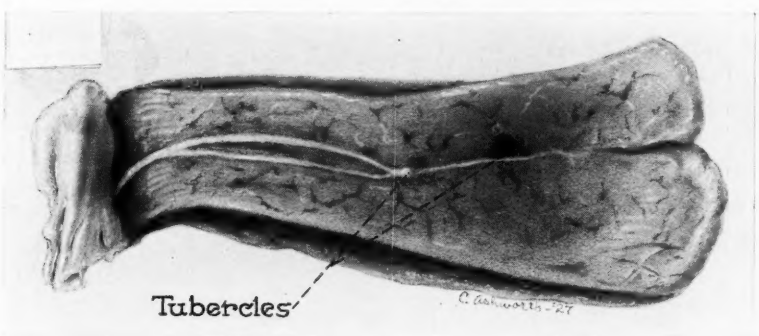

FIG. 5. Specimen of lung, showing the same distinct proliferative condition of the lymphatic vessel extending from a tubercle to the region of the hilum. A small calcified tubercle is seen within the lymphatic vessel.

beyond this for a short distance the fibroblasts appeared to have some circular arrangement. Throughout the entire length of this lymph-vessel a remnant of the lumen persisted.

The second case of my series was found in a man, aged thirty-eight years. On the pleural surface of the upper lobe of the left lung a tubercle was seen surrounded by an area of heavy fibrosis containing considerable anthracotic deposit. The adjacent node of the hilum showed considerable calcification. This patient had died from appendiceal abscess and peritonitis. A history of tuberculosis was not obtained.

Between the primary tubercle and the calcified node of the hilum, the same kind of grayish-white, elevated vessel was seen on the pleural surface. At a distance of 2.5 cm. from the primary tubercle, a small calcified nodule was

found within this vessel. At this point the channel became bifurcated, and ran in parallel lines toward the hilum. The two channels became united at a point about 1.5 cm. before the vessel entered the tissues of the hilum where the calcified node was located (figure 5).

Sections of the lymph-vessel taken from various portions for microscopic study revealed the same condition throughout. The lumen in nearly all portions was completely obliterated. In proximity to the primary tubercle, the vessel was irregular in shape; the proliferation occluded all but a narrow elongated portion of the lumen, which appeared filled with a homogeneous

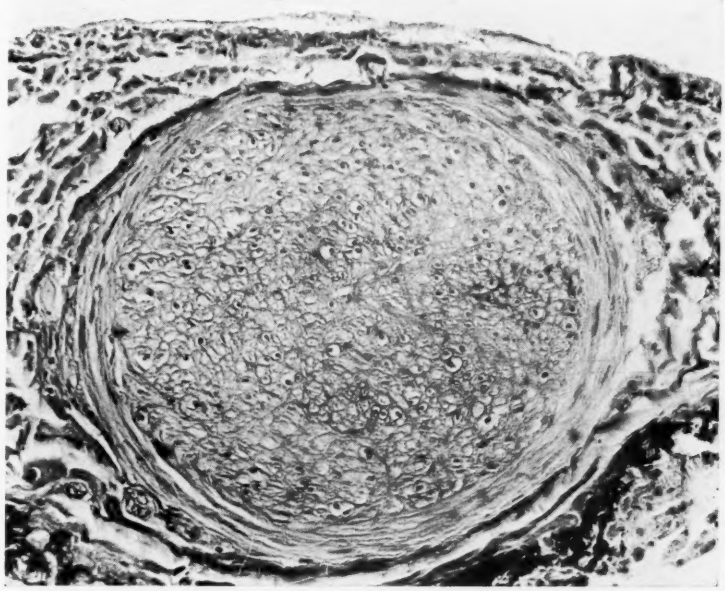

FIG. 6. The lymphatic vessel beyond the tubercle. Dense fibrous-tissue proliferation is seen around the wall. The lumen is entirely occluded by proliferative tissue which shows marked vacuolization. Fibrous tissue is also replacing the original proliferative cell (× 150).

acid-staining substance, probably coagulated lymph. Surrounding the tubercle and the lymph-vessel, except at the pleural margin, was a region of heavy fibrosis which contained a marked anthracotic deposit. Immediately after leaving this fibrotic area of the primary tubercle the vessel became rounded, and the lumen completely occluded; in the wall was an increased amount of fibrous tissue, circularly arranged.

A further change was noted after union of the two vessels. There were vacuoles in the fibroblasts. Many of the nuclei had disappeared, but those which remained presented the same irregular, ovoid or rounded contour and

still were deeply staining (figure 6). Radiating bands of fibroelastic tissue made their appearance. The vacuolization and the beginning fibrous tissue replacement I consider as evidence of degeneration of the region of fibroblastic proliferation.

My third case of lymphatic involvement was that of a woman, aged thirty-three years, in which necropsy revealed carcinoma of the pyloric end of the stomach.

In the right lung, on the interlobar surface of the upper lobe, was found a large subpleural tubercle over 1 cm. in diameter. This was 5 cm. from the region of the hilum, which contained a lymph node with two calcified tubercles. Extending from the primary pulmonary tubercle and apparently connecting with the node was the same type of grayish-white, cord-like lymph-vessel seen in the other cases, and elevated above the pleural surface. Along its

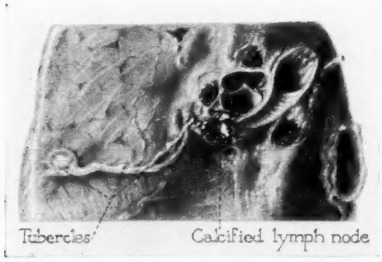

FIG. 7. Specimen of similar proliferated lymphatic lying between a primary tubercle and a tuberculous lymph node. Three secondary tubercles are seen along the course of the lymphatic

course were three smaller tubercles, the last one immediately adjacent to the node of the hilum; so that on serial section through this area the tubercle was seen extending into the node. Bifurcation of the lymph-vessel occurred, and just before it entered the last tubercle the two branches again became one (figure 7).

Serial sections were made of the lymph-vessel, beginning at its origin at the primary tubercle and extending into the node of the hilum. Immediately after it had left the primary tubercle, it was found as a rounded structure, with a heavy fibrous-tissue wall and with the lumen obliterated. The fibroblasts which filled the lumen did not present a typical arrangement. The nuclei appeared irregularly ovoid or rounded, and they were deeply stained. Vacuolization was again seen, and in some areas evidence could be detected of a proliferation of fibrous tissue in fine radiating bands which extended from the periphery.

Canalization was seen in the central part of the proliferated tissue and the channel was lined with a single layer of endothelium. The cells which made up this endothelium, instead of appearing flattened, as are those which are usually seen, were rounded and irregularly disposed. The nuclei were close together and rounded in contour (figure 8). The appearance of the cells was that of newly formed tissue, and the canalization of the occluded lymphatic which was under way was probably similar to that which occurs in the obliterative diseases of the vascular system. The canalization extended to the first tubercle in the lymphatic pathway and then reappeared just before

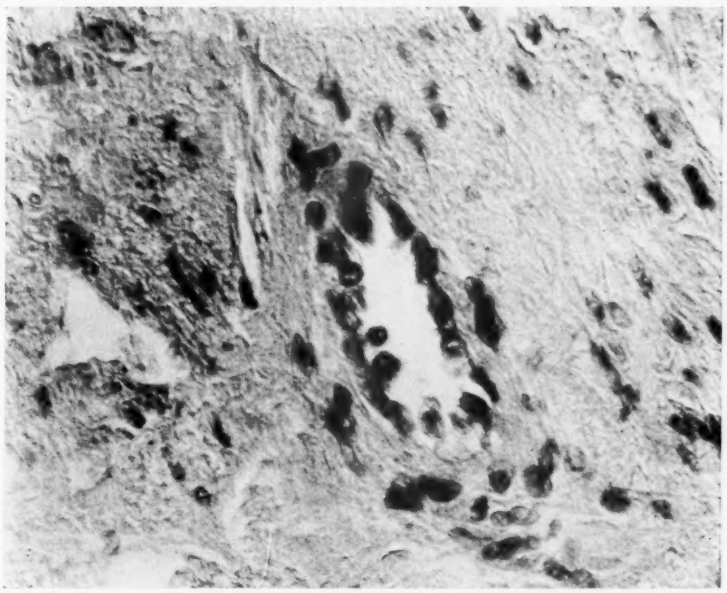

FIG. 8. Specimen showing the detail of the canalization. The endothelial lining is a single layer. The cells appear more rounded and are irregularly placed, indicating newly formed tissue (× 600).

bifurcation of the channel; it continued in one pathway until it reached the last tubercle before the node of the hilum.

With Weigert's elastic-fibre stain was seen heavy fibroelastic tissue evidently in process of replacing the degenerating fibroblasts. It appeared in radiating bands extending from the periphery and was especially heavy around the areas of canalization.

As the lymphatic entered the region of the first secondary tubercle, the definite circularly arranged fibrous wall disappeared, and was replaced by dense, irregular fibrous tissue which encircled the lymph-channel and the tubercle.

A few small areas of lymphocytes were found in this tissue. Beyond the tubercle the circular fibrous-tissue wall again appeared and was the heaviest found, occupying nearly half of the diameter of the vessel. The lumen was entirely filled with the fibroblasts. The cytoplasm of the cells was markedly vacuolated, and bands of fibroelastic tissue were seen (figure 9).

Shortly beyond this area the fibrous-tissue wall was thinner, and canalization again was noted. The evidence of degeneration of the proliferated cell disappeared, whereas the vessel was enlarged and soon became bifurcated. As the vessel entered the tubercle its appearance changed. The circularly

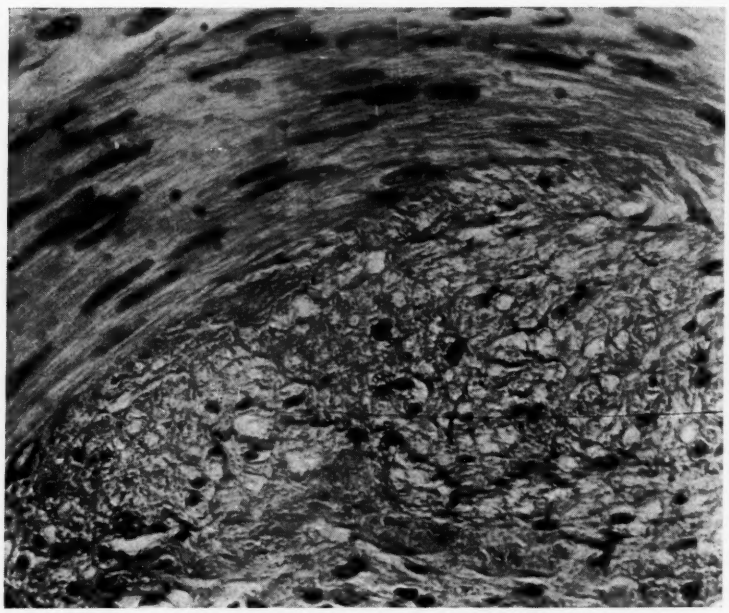

FIG. 9. Marked vacuolization of the fibroblasts is seen, with strands of fibroelastic tissue replacing these cells (× 350).

arranged wall of fibrous tissue became a looser, heavier tissue with an appearance as if it had become hyalinized. The lumen of the vessel was partly patent, and contained a loose reticular connective-tissue network in which lymphocytes were seen. The canals were lined with flattened endothelial cells which continued along the remaining small distance to the calcified tubercle, where all characteristics of a channel were lost.

The last case of the series was found in a woman, aged seventy-nine years. The clinical cause of death was senility and cerebral thrombosis. No history of tuberculosis had been recorded.

Apical scarring was present, and a large calcified plaque, measuring 4 by 3 cm., was found adjacent to the area of scarring. Over the surface of the lung, a number of small calcified nodules were present, all resting subpleurally. A node of the hilum was found which contained a large calcified tubercle. On the mediastinal surface of the upper lobe of this lung there was a calcified tubercle measuring about 6 mm. in its longest diameter. Extending from this tubercle toward the hilum was a series of grayish-white, rounded, elevated lymph-vessels of firm consistence. They were arranged in the form of an irregular network. One channel appeared in its course toward the region of

FIG. 10. Smaller lymph-channels, showing a large amount of transformation into hyaline material (× 60).

the hilum as the main trunk from which the other vessels ran or with which they were united.

Through several areas sections were taken for microscopic study. The lymph-vessel which acted as the main channel between the tubercle and region of the hilum presented the same picture throughout its entire course. It appeared as a rounded, dilated vessel, with the lumen entirely occluded. Overlying the vessel the pleura was seen invaginated and thickened by an increase in fibrous tissue which extended down to the vessel. In a few places in this region of fibrosis some anthracotic deposit was noted. The wall, as in all

preceding cases, did not possess an endothelial layer. The lumen, which was completely obliterated, presented a different picture from that in any of the other cases. The number of fibroblasts was greatly diminished. These evidently had been transformed into a hyaline substance which was seen as a grayish, slightly blue, wavy and homogeneous mass lying between the remaining cells.

A more marked transformation into hyaline substance was noted in some of the smaller vessels of the network, on the mediastinal surface (figure 10). One of these channels, in which the lumen was completely obliterated, contained, throughout its entire length, only a few nuclei, which appeared but faintly stained and granular, indicating a degenerative process. The substance replacing the fibroblasts could be seen to be hyaline.

In the series which I have just presented the proliferative changes within the lymph-vessels were manifestly the direct result of tuberculous infection. I would affirm, therefore, that this condition can be due only to tuberculosis. The possibility that nontuberculous infection may bring it about must be granted, although proof of this theoretical exception has not been found during the course of my studies.

I have tried to present the steps which occur in the obliteration of the lymph-vessels. After the beginning of the tubercle, toxic products in the form of bacilli or tuberculin, or material produced by the action of the bacillus on the tissues of its host are drained away, through the lymphatic channels, by the most direct route to the hilum. The endothelial lining, having acquired a special sensitivity to these products, proliferates, resulting in the formation of thrombi. The cells which compose these thrombi are primarily fibroblasts, but occasionally cells ordinarily found in the lymph are also enmeshed. Fine fibrin may interlace this structure. Further changes indicate that these fibroblasts continue to proliferate to such a degree as to exclude all other types of cells. The lymph-vessel becomes widely dilated and is packed by a solid mass of these cells. Tubercles also may be formed along the course of the vessels in which this proliferation has taken place, but they pursue their usual course and offer no interruption or variation.

No true organization of proliferated tissue occurs, and the older processes, in consequence, sooner or later undergo degenerative or retrogressive changes. The main change, it appears, is degeneration, which has been shown to be in the form of vacuolization of the cells. The nuclei, in regions in which this vacuolization is present, are diminished in numbers. There also appear strands of elastic-tissue fibres apparently

originating from the vessel wall. Canalization also may occur and, when seen, the channel is lined with newly formed endothelial cells which are irregularly placed and of rounded formation.

The other retrogressive change, which was found in the last case presented, was hyaline transformation of the fibroblasts. This was found in some of the smaller vessels to have transformed the entire cellular content of the lymphatic, with the exception of a few remaining nuclei, into a hyaline mass.

In the case in which the proliferative change was found to extend from the area of tuberculous scarring at the apex, I have considered it to be of more recent formation. No vacuolization had taken place; practically no fibroelastic tissue was noted, even when special methods of staining were employed, and no canalization had so far occurred. In addition, I believe, the condition which results from a secondary tuberculous focus gives greater proof of selective endothelial sensitivity, for involvement of lymph nodes does not usually result from a secondary focus. When proliferation occurs along the lymph-vessels from such an area, the inference is that sensitivity must have played a greater part than usual in producing the proliferation, for, under such conditions, stasis of the lymph probably would have been less than that which commonly occurs in involvement of the lymph nodes. As a designation for these proliferative phenomena, which occur within the lymph-vessels and which result first in thrombus formation and later in obliteration of the lumen, I wish to suggest the term *thrombo-lymphangitis obliterans*.

CONCLUSIONS

A thrombus occasionally forms in lymph-vessels which drain the area of a tuberculous focus. It is due to sensitivity of the endothelial lining of the vessel, and results in proliferation of the endothelial cells with a formation of fibroblasts. The formation of the thrombus continues until the lumen of the lymph-vessel is densely packed with these fibroblastic cells. Following this and without organization, degenerative or retrogressive changes occur. Usually these changes appear as a vacuolization and replacement of the cell by fibroelastic tissue, or by a transformation of the fibroblast into hyaline material. Canalization of the occluding mass also is seen. This proliferation is entirely separate from the formation of tubercles within the lymph-vessel, which also may occur. The type of proliferation, although it is due to the stimulation of tuberculous products, is not distinctive, and in itself it would not be known to be of tuberculous origin.

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REACTIONS OF THE SUBCUTANEOUS CONNECTIVE TISSUE TO EXPERIMENTAL TUBERCULOSIS IN THE GUINEA PIG[1]

MAUDE L. LINDSEY[2]

This study was planned with the purpose of determining the origin, in the early stages and under maximal stimulation, of the cells of anatomical tubercle, which, it is assumed, represent the defense of the body against the infection.

Virchow described specific cells of tubercle found in the presence of tubercle bacilli, and having origin from the body of the host. Maximow (55) and others recognized the epithelioid cell as not only the most constant constituent of specific tubercle, but also as the most specific type of cell of the exudative type of reaction to tubercle bacilli.

Maximow (55) and MacCallum described the tubercle as a zonal arrangement of cells, epithelioid cells, almost always associated with multinucleated giant cells of the Langhans type which form the inner zone. A layer of lymphoid cells which may or may not be accompanied by polymorphonuclear leucocytes forms an outer zone of the mass, which is supported by a fibrin mesh and a newly formed framework or reticulum. Previously existing blood-vessels are obliterated.

Maximow mentioned the presence of common fibroblasts in the surrounding connective tissue; tubercle bacilli may be scarce or totally absent.

The epithelioid cell is described as a pale, polyhedral cell, with abundant cytoplasm having a cytocentrum and a large, pale nucleus. Castrén mentioned the marked similarity of these cells, with their one, two or three large nucleoli, to "stimulated fibroblasts," from which a distinction is often doubtful. Narrow processes connecting adjacent cells have been described by Castrén and by MacCallum.

Theories of origin of the epithelioid cell are various, based on studies

[1] Abridgment of thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Arts, 1928. Work done under the direction of Dr. Hal Downey, Hematological Laboratory, Department of Zoology, University of Minnesota, Minneapolis, Minnesota.

[2] Fellow in Pediatrics, The Mayo Foundation, Rochester, Minnesota.

of human pathological material, and on *in vivo* and *in vitro* experimental studies. More recent efforts to differentiate cell types by means of vital and supravital technique with operative human and experimental animal material have been responsible for new and altered theories as to identification and origin of these cells.

Metschnikoff, Gilbert, Buday, Homen, Borrel, Cunningham, Sabin, Sugiyama and Kindwall, and Wallgren support the theory of the haematogenous origin of epithelioid cells. Borrel found the primary local intravascular polymorphonuclear reaction replaced after three days by a collection of large monocytes. Cunningham, Sabin, Sugiyama and Kindwall, as the result of studies, by means of supravital staining, of blood and tissues of tuberculous animals and of blood of tuberculous patients, maintain that the blood monocyte is the reacting cell which becomes transformed into the epithelioid cell. Cash, after similar studies, refused to so interpret his data which were in agreement with theirs. Lewis, Willis and Lewis recognized the two supravitally reacting types of cells found in tuberculous lesions (clasmatocytic and monocytic), but they noted many intermediate types of reactions. Foot (31) recently retracted all former statements (29) with regard to the endothelial origin of the epithelioid cells, and, as the result of supravital technique, he has concluded, with Cunningham, Sabin and Doan, in favor of the monocytic origin of these cells.

Miller (62), McJunkin, Mallory (50), Permar and Kockel consider the endothelium as the source of epithelioid cells. Baumgarten and Orth apparently included the endothelium with other "fixed tissues," as did Wallgren with histiocytic and fibroblastic proliferation. Castrén derived the epithelioid cell chiefly, if not exclusively, from fibroblasts.

Reticular-cell origin has been demonstrated by Evans, Bowman and Winternitz in liver tubercles, by Joest and Emshoff in lymph-node tuberculosis, and by Goldmann, Kiyono and Oppenheimer in experimental tuberculosis. Kiyono included fibroblastic, as well, and was not able to exclude lymphoid and plasma-cell origin. Maximow (55), in studies of cultures of lymph nodes inoculated with tubercle bacilli, considered that both lymphocytes and reticular macrophages gave rise to epithelioid cells. MacCallum suggested the possibility of a multiple genesis of this type of cell, including fibroblasts whose genetic relation is suggested by the coherent character of the reticulum-producing tubercle. Aschoff considered that the fibrocytes without doubt participate in building up tubercles, but the tissue histiocytes (connective-tissue wandering cells)

are primarily concerned. Virchow derived the tubercle from the "connective tissue;" Kockel associated connective-tissue cells and endothelium, and Wallgren, von Fieandt, Castrén and Timofejewsky and Benewolenskaja assigned to fibroblasts a formative rôle in tubercle-formation. Stewart and Rhoads found accumulations of "endothelial leucocytes" about fat, in intracutaneous tuberculin reactions, but did not discuss their origin. The epithelial origin of epithelioid cells was suggested by Lubarsch and in references given in Foot's most recent paper.

By means of vital and supravital technique, an effort at physiological differentiation of morphologically similar cell types has been made by Aschoff, Kiyono and others. The histiocytes (resting wandering cells, clasmatocytes, reticular cells of various organs, and lymphoid-tissue cells which take up the dyes in a certain arbitrary manner) are distinguished in this way from fibrocytes, parenchyme cells of various organs, and emigrated blood leucocytes which take the dyes less readily or in a different form.

As a result of this basis for differentiation, Stewart and Parker, by the use of collargol injections, concluded that epithelioid cells were of clasmatocytic rather than monocytic origin, the character and distribution of the stored granules in these cells resembling that seen in clasmatocytes. The fact that the amount of dye stored in the tubercles of the various organs varied with the relative quantities of component histiocytes in the respective organs was assumed to be evidence of the local origin of these cells.

Aschoff, somewhat in agreement with the latter authors, believes that the tubercle represents a histioblastic reaction, although he admits that in organs with scarce histiocytic content, as in the lungs, the fibroblastic reaction might delay the histioblastic reaction. He is of the opinion that vital storing is of no value in studying the late stages, since in caseation the vitally-stored dye is lost.

Foot (29), finding only ink granules in tubercles after the simultaneous injection of india ink and niagara blue, considered that the reticulo-endothelial origin of epithelioid cells was conclusively excluded in favor of the endothelial origin.

Downey (23) proved, however, the nonspecificity of *intra vitam* storage of dyes for all types of cells.

Cunningham, Sabin, Sugiyama and Kindwall, by means of the supravital technique, found an increase in blood monocytes and in monocytes of the tubercle, with intermediate stages between the monocyte and the

epithelioid cell. On this experiment and on their distinction (76) between clasmatocytes and monocytes as two distinct types of connective-tissue macrophages they base their theory of the monocytic origin of the tubercle. By the same means they demonstrated (75) a pathognomonic response in the lung after intravenous inoculation of the rabbit with tubercle bacilli within twenty-four hours, and in the liver and other organs within six to fourteen days. They concluded that the presence and relative numbers of clasmatocytes and monocytes, respectively, indicate the extent of the process, the clasmatocytes representing the destructive reaction, the monocytes acting as a protective host to the invading microörganism. In a study (74) of the effects of subcutaneous injection of the protein and the phosphated fractions, respectively, of chemically analyzed tubercle bacilli, the same authors found a specific response to each, the protein fraction producing a clasmatocytic reaction, and the phosphated fraction the epithelioid and giant-cell reaction. This question recalls the disagreement of Bergel and Aschoff and Kamiya regarding the specificity of cellular reactions to injected fats, proteins and alkalies, a specificity which the latter authors deny.

Lewis and Lewis distinguished clasmatocytes, epithelioid cells, and giant cells originating from mononuclear leucocytes in cultures of normal blood. They consider these forms as temporary variations of the same cell type. Lewis and Webster found the same cells in normal and pathological lymph-node and lung spreads and tissue cultures. They demonstrated in the tubercle all stages between monocytes and epithelioid cells, between clasmatocytes and epithelioid cells, and between monocytes and clasmatocytes.

As constituents of normal loose connective tissues, Schäfer included clasmatocytes, which he described as elongated or irregular cells having elliptical nuclei and granular, vacuolated cytoplasm. He believed that these cells may represent mesenchyme cells that are less differentiated than the fibroblasts, which he described as lamellar, plaque-like, or branched cells, whose cytoplasm may be slightly granular or at times fibrillated. Maximow (52), in describing the cell forms of the normal connective tissues, included fibroblasts, mast cells, clasmatocytes, lymphocytes, plasma cells, eosinophiles, and fat cells. The fibroblasts according to him, represent a terminal differentiation of mesenchyme, whose function was finally determined when the separation from the mesenchyme stem-cell occurred, with an accompanying limitation of potentialities to the reproduction of their kind in growth and inflamma-

tion, without loss of morphological characteristics. He distinguished clasmatocytes from fibroblasts by their smaller, darker, irregular, more darkly staining nucleus without nucleoli and their dark, sharply-bounded or very irregular outline. These cells, occurring everywhere in the connective tissue, are more numerous in the vicinity of blood-vessels and fat cells. Morphologically, they occupy a position between the fibroblasts, on the one hand, and the tissue lymphocytes, between which and clasmatocytes there are many intermediate forms, on the other. Recently Maximow (56) postulated the existence throughout the connective tissues of undifferentiated mesenchyme cells, not morphologically distinguishable from fibroblasts, but, in contrast to fibroblasts, capable of full developmental and transformational potentialities. Alfejew (1) is in agreement with Maximow as regards the origin and specialization of fibroblasts.

Awrorow and Timofejewsky observed the transformation of lymphocytes, in cultures of leucaemic blood, into spindle-shaped and stellate fibroblasts, but Hirschfeld, and Hirschfeld and Klee-Rawidowicz, who have also studied cultures of leucaemic and normal blood, claim that fibroblasts are transformation forms of macrophages which, in turn, are derived from monocytes and not from lymphocytes. Maximow (53) produced the same changes in peritoneal macrophages and in polyblasts. Carrel (51) noted the formation of fibroblasts from connective-tissue macrophages, and Carrel and Ebeling from large mononuclear leucocytes in chicken blood, where the newly formed cells exhibited the usual supravital differentiation characteristics of numerous transitional forms between monocytes and fibroblasts. Policard and Desplas derived fibroblasts from lymphocytes in granulating wounds. Dubreuil saw them originate from large mononuclear blood cells which, by way of transformation into clasmatocytes, later formed fibroblasts. Renaut assumed that fibroblasts found in an epithelial-lined cyst had formed from immigrated round cells. Maximow (55) found fibroblasts originating from reticulum and from blood-vessel endothelium. He also observed (58) the development *in vitro* of nongranulated blood leucocytes into fibroblasts, as did Bloom in cultures of nongranulated mononuclear cells from thoracic-duct lymph.

Aschoff included fibroblasts in his reticulo-endothelial system, in the broader sense, based on their affinity for vital dyes, to which they react only when concentrated, and to varying degrees.

Renaut believed that the function of connective-tissue cells is that of

internal secretion, and that they originate from lymphocytes. Loeb concluded that fibroblasts and lymphocytes may be regarded as organs of attack, which lie quiescent under ordinary conditions. Murphy's observations agree with those of Loeb.

In experimental studies of the connective tissues of living animals, Maximow (54) has shown that in aseptically inflamed tissue fibroblasts react readily to roentgen rays. He interpreted this as disproving the assumption that the least specialized cells are most easily affected by the roentgen rays. He could not explain the presence of polyblasts in such great numbers in the exposed areas at all stages, when there are so few lymphocytes, to which he considered the polyblasts in direct genetic relationship. He assumed that the few lymphocytes which are present have emigrated from the blood-vessels after the destruction and dissolution of the original lymphocytes by the roentgen rays.

Kingsley decided that lymphocytes in loose connective tissue originated from cells indistinguishable from fibroblasts. He was of the opinion that loose connective tissue retains its embryonic prospective developmental potencies throughout life.

Von Möllendorff and von Möllendorff, by means of a special technique, were able to demonstrate, in connective-tissue spreads from animals treated with trypan-blue, that histiocytes are a stimulation form of fibrocytes, between which cells syncytial-plasma connections exist. This tissue, of which the fibrocyte is the primarily reacting cell, reacts as a system, the varying degrees of dye storage representing the relative inability of individual cells to destroy the dye after ingestion. Histiocytes, macrophages, or polymorphonuclear leucocytes represent the various types or degrees of reaction of individual cells in this system. The authors believe that the small round cells originating from fibrocytes develop into polymorphonuclear cells, and that the large round cells are transformed into macrophages or produce more fibrocytes.

Lewis observed the loss of the stellate processes of mesenchymal cells of explanted embryo-chick heart, forming rounded, mesothelial cells. He decided that mesenchyme is not a syncytium, but an adherent reticulum, whose cells may take the stellate or the rounded form.

Bauer found the connective-tissue cells reacting to pyrogallic acid with a rounding of the protoplasm and severing of connections with neighboring cells. The formation and extension of fluid blebs in the cytoplasm, which became granular, and the development of a dark, refractile nuclear membrane were considered evidences of severe stimulation.

Lewis and Webster found, in tissue cultures of human lymph nodes, that phagocytosis was more active in those nodes in which an abundance of scar-tissue is more often found, as in Hodgkin's disease, sarcoma and chronic or tuberculous lymphadenitis, than in normal or carcinomatous nodes. They observed that endothelial cells stand in an intermediate position between wandering cells and inactive fibroblasts.

Maximow (53), (55) could not see any evidence of a transformation of fibroblasts to wandering cells; the fibroblasts, which were easily distinguishable from reticular cells, in lymph-node cultures, becoming much more actively "mitotic" than the amoeboid cells which appeared at the end of two days. Stellate cells rounded up and accumulated fat globules after seven days. This process Maximow interpreted as a regressive change.

It is notable, however, that, in cultures of lymph nodes inoculated with tubercle bacilli, Maximow (55) noted an "embryonic" transformation of the fibroblast, which he considered a "specific" reaction of the fibroblast to the tubercle bacillus. Although he did not admit a further transformation of fibroblasts, he believed that certain of these cells (which he assumed arise from reticulum and blood-vessel endothelium) may "temporarily acquire a round shape." He distinguished these cells from the epithelioid cells of "reticular origin" by the absence of the greenish pigment usually found in epithelioid cells, and by the character of their nucleus. The absence of pigment in young polyblasts of presumed reticular origin he considered as due to loss of pigment during mitotic division. The fact that tubercle bacilli are usually present in these cells he assumed to be evidence of their reticular origin. However, he admitted that the fibroblasts round off easily in the omentum, and he could not exclude the possibility of epithelioid-cell and giant-cell formation from them. He explained this discrepancy in his interpretation of fibroblastic activity on the basis of the more embryonic character, and hence greater developmental potentialities, of the fibroblasts of the latter situation. He considered that activity abruptly ended with the reversion of fibroblasts elsewhere to the embryonic type. Untransformed and polyblastic lymphocytes engulfed or surrounded clumps of bacilli; plasma-cell formation was inhibited.

Fischer observed the sudden spontaneous transformation of a pure culture of fourteen-day-old fibroblasts into rounded, amoeboid, phagocytic cells. He also noted an equally sudden return to the stellate form, with a second assumption of macrophagic characteristics, when tuberculin

was added to the tissue culture. He did not assign a causative rôle to the tuberculin, but stressed the significance of the reversibility of the fibroblast in the "leucocyte-monocyte-macrophage-to-fibroblast" system.

Evans and Scott, in a study of vital-dye storage in loose connective tissue, found that this method was not a criterion for distinguishing the two types of constituent cells which they presumed to exist; namely, the functionally different fibre-forming and phagocytic cells. With chronic staining, the storage within fibroblasts took the form identical with that assumed at certain stages of typical clasmatocytes and polyblasts. The authors noted a physiological dissimilarity of the two types, their explanation of storage in fibroblasts being that it is due to the failure to decolorize the ingested dye as quickly as in the case of the macrophages, a view which von Möllendorff and von Möllendorff share.

Sabin, Doan and Cunningham, in discussing these observations, assumed that the fibroblast is forced to react to a condition abnormal to it but normal to the macrophage.

Knake observed a rounding off of fibroblasts in preparations of connective tissue from rabbits treated with india ink. She believed that these cells became histiocytes or, by the development of granules and polymorphous nuclei, polymorphonuclear leucocytes. More leucocytes were formed by the amitosis of fibrocytes. Local changes outside blood-vessels preceded the evidences of leucocytic emigration. In the transformation of dye-containing fibroblasts to leucocytes, the diffusely imbibed dye was considered by Knake to have been released in the form of granules. In regions where histiocytes were abundant she observed that the fibrocytes were reduced in number by a transformation to histiocytes through amitosis. Benninghoff regarded these forms as evidences of protection against a menaced equilibrium, including cells with ring-nuclei and round cells that had separated from the fibrocyte net after it had assumed a histiocytic form.

Bruni believes, with von Möllendorff and von Möllendorff, that the blood-connective-tissue apparatus should be considered a part of the reticulo-endothelial system, but he does not favor their view as to the fibrocytic origin of tissue lymphocytes and tissue leucocytes. In the regeneration of partially extirpated thymus Popoff recently found that "wherever the connective tissue comes in contact with epithelium the cells of the former become mobilized as large, medium-sized, and small lymphocytes." Carrel and Ebeling found that, in comparing cultures of tissue macrophages with cultures of blood monocytes, the difference

in size of the cells of the latter culture as compared with those of the former soon disappeared and the cells of both groups were equally affected by toxic agents.

In *in-vitro* cultures of embryonic connective tissue of lower vertebrates Chlopin found that the power to develop varied morphological and physiological elements was retained by the connective tissue. Stellate or spindle cells of fibroblastic type developed into amoebocytes or were rounded off by a pulling in of all branches. The author produced macrophages in young and adult mesenchyme by means of trypan-blue; by a foreign-body stimulation of the mesenchyme he produced phagocytic polyblasts, which developed into giant cells; and he observed a differentiation of "*Tonofibrillen*" in fibroblasts. These changes he considered as common phenomena in aseptic inflammation in the adult.

Alfejew (1) and Maximow (57) assumed that histiocytes or resting wandering cells arise, in adult tissue, from undifferentiated mesenchyme cells, whose morphology is identical with fibroblasts, or from preëxisting clasmatocytes.

Evans and Scott derived tissue macrophages from endothelium and from mononuclear blood cells; Benninghoff believed that round cells separate off from the fibrocytic net; Sabin, Doan and Cunningham derive clasmatocytes from vascular endothelial cells.

Among the most recent experimental observations of the tuberculous process, Metalnikov and Secretiva, in a study of the fate of subcutaneously and intraperitoneally injected tubercle bacilli, found that the polymorphonuclear leucocytes were active for the period of the first four days after injection; the mesolymphocytes and macrophages took the field from the third to the seventh days, and the lymphocytes predominated only after seven or eight days. This cycle was observed consistently.

Timofejewsky and Benewolenskaja, by inoculation of cultures of acute leucaemic blood, found the myeloblasts markedly phagocytic and destructive of engulfed tubercle bacilli, forming epithelioid cells. Growth of the microörganisms and development of granulocytes, clasmatocytes and fibroblasts in the cultures were retarded. Inoculated cultures of blood from patients with chronic myelogenous leucaemia gave results similar to inoculated cultures of normal blood leucocytes.

Evidences of fibroblastic activity, as studied *in vitro* by Smith, Willis and Lewis, and by Smyth were limited to phagocytosis of tubercle bacilli. Lang noted less proliferation of fibroblasts in lung tissue inocu-

lated with tubercle bacilli than in noninoculated tissue cultures. He derived epithelioid cells from macrophages originating from mobilized septal cells. In certain cases, however, the septal cells formed a mesenchyme like syncytium, a reaction which the author assumed to be the result of diffusion of the toxins from the bacillus. He found that fibroblasts, lymphatic endothelium and septal cells became embryonic. Evidence of fibroblastic transformation of histiocytes was not noted.

MATERIAL AND METHODS

The series of animals included in this report consist, with the exception of the twelve-hour and eighteen-hour stages, of guinea pigs less than one week old. The excepted pigs were about one month old, and had received 1 cc. of 1 per cent trypan-blue intraperitoneally one week previous to inoculation with tubercle bacilli. This series was inoculated by the subcutaneous surgical implantation of a clump of tubercle bacilli, strain H37 Saranac Laboratory, taken from the culture medium. Inoculation in all but the nine-day and fifteen-day series was in the thigh, the two exceptions being inoculated in the upper midventral line of the abdominal wall. For the two-day, three-day, and four-day stages, there were animals of corresponding stages which had been given 1 cc. of 1 per cent trypan-blue intraperitoneally twenty-four hours before they were killed.

The animals were killed twelve, eighteen, forty-eight, seventy-two and ninety-six hours, and nine and fifteen days, respectively, after inoculation with the bacilli. The skin and subcutaneous tissue enclosing the lesion were taken with their underlying muscle. In some of the animals tissue spreads were made by the usual technique of teasing thin layers on a coverslip, and they, with blocks of subcutaneous tissue, were fixed in Zenker-formalin solution. The blocks were embedded in celloidin, and sections were stained with Dominici's stain. In a few instances the Pappenheim-Kardos stain was used, as well as an occasional Ziehl-Neelsen-eosin-azure stain for tubercle bacilli. A few sections were also stained with Delafield's haematoxylin, Giemsa's stain, and Mallory's eosin-methylene-blue. Best general results were obtained with Dominici's stain, and hence it will be used as the standard to describe the series, which includes 11 animals.

DETAILS OF INVESTIGATION

Guinea Pig 1: Twelve-Hour Stage: The lesion, occupying a space about the size of two low-power fields, was composed of clumps

of tubercle bacilli and dense collections of polymorphonuclear leucocytes, which were rather distinctly walled off by fibrin. Extending along the loose connective-tissue septa was extensive oedema, with marked accumulation of reacting and emigrated cells. In some sections there was a spreading surface extending out about one and a half low-power fields from the edge of the lesion in the form of the advancing margin of tissue cultures. About certain blood-vessels were dense accumulations of polymorphonuclear leucocytes and small lymphocytes with many small polyblasts.

Study with the oil-immersion lens showed the shrunken, densely packed, and pycnotic polymorphonuclear leucocytes penetrating the lesion between the bacillary clumps. Shrunken polyblasts with faintly retained nuclear pattern were found near the edges of the lesion. There were very few lymphocytes within the fibrin capsule.

The blood-vessels, filled with an abundance of polymorphonuclear leucocytes and, in case of some smaller vessels, loaded with lymphocytes, did not show any evidence of endothelial activity, except for occasional mitoses. There were many polymorphonuclear leucocytes and lymphocytes in tissues about certain larger vessels.

The fibroblasts at this stage were definitely stimulated. Plate 1, figure 1, shows the occurrence in a single field of rounding-off, rounded, and shrinking fibroblasts, which at the same time show markedly hypertrophic nucleoli. This field was selected from the edge of the exudate near an area of condensation of fibroblasts lying adjacent to a mass of fat cells. Similar reactions could be seen near muscle-bundles.

The more distant, less loosely constructed connective tissue showed thickening of the cell, a markedly basophilic cytoplasm, and occasionally a prominent small centrosphere. These cells appeared to thicken by drawing in their normally slender processes from between the collagen bundles, or by swelling of the cytoplasm. With increased basophilia, the cytoplasm became finely granular, the boundaries of the more stimulated cell being made out only by the extent of the granules. As the cells were further stimulated, the nuclei became paler, the chromatin more diffusely distributed, and the one, two or three nucleoli became distinct, large, round, red-staining bodies. With this further swelling of the cell, the early basophilia diminished. A few of the resting fibroblasts and cells with more condensed clasmatocytic nuclei were to be seen as round cells, and between these and lymphocytes a complete series was not to be found.

In more oedematous portions of the tissues were prominent stellate, comet-like, or spindle-shaped cells, whose form appeared to be dependent on retained attachments. Portions of the margins of these cells were ragged or frayed, giving the appearance of having pulled away from attachments.

Phagocytosis of polymorphonuclear leucocytes was very active in incompletely changed fibroblasts of this stage, spindle-shaped cells in certain instances containing as many as three cells tightly crowded in their cytoplasm. Phagocytosed cells could be seen in the rounding and the rounded-off fibroblasts. Occasionally a mitosis of fibroblasts was seen. Amitosis was rare.

Plate 1

FIG. 1. (Twelve-hour stage.) *a*, *b*, *c* and *d* are early stages of rounding-off of fibroblasts whose nucleoli have hypertrophied; *d* is a condensed nucleus of the same type; this cell is an approach to a polyblast, of type *g*; *e* is a small lymphocyte from the same slide; *f* is a polyblastic lymphocyte; *g* shows marked phagocytosis by larger polyblasts.

FIG. 2. (Eighteen-hour stage.) Fibroblast separating from its connections.

FIG. 3. (Eighteen-hour stage.) Fibroblasts separating from their connections, showing more hypertrophy of the nucleus.

FIG. 4. (Forty-eight-hour stage.) Plasma connections between various types of cells. *a* is an hypertrophied fibroblast; *b* is a lymphocytic type of cell whose nucleus is similar to that of the clasmatocyte, *c*; *d* is a free cell of type *b*.

FIG. 5. (Nine-day stage.) Cells taken from the same field: *a* is a resting fibroblast; *b* is a macrophage with fibroblastic nucleus; *c* is a chain of cells along a fat space; the upper two dark cells are basophilic fibroblasts, the next pale cell is a fibroblast, the lower two cells are a polyblast and a monocytic cell of which many similar wandering cells are to be found; *d* is a larger polyblast, and *e* is a clasmatocytic macrophage with dark, granular nucleus.

Comparatively few clasmatocytes were to be distinguished in the slightly irritated areas. They were indistinguishable in the oedematous tissues.

There were two groups of polyblastic cells, consisting of small polyblasts, which were present in about the same numbers as the polymorphonuclear leucocytes and were only slightly larger than small lymphocytes, and the larger polyblasts, which were much less numerous than the first type. Some of these resembled large lymphocytes, and others had larger monocytic nuclei.

Lymphocytes were as abundant in this stage as the numerous polymorphonuclear leucocytes. As soon as they left the blood-vessel, they assumed polyblastic shapes, and there was apparently no increase in the amount of cytoplasm. A large proportion of the medium-sized poly-

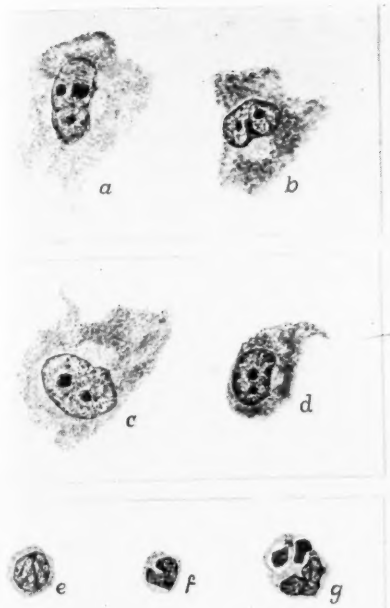

Fig. 1

Fig. 2

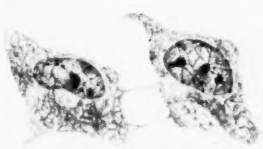

Fig. 3

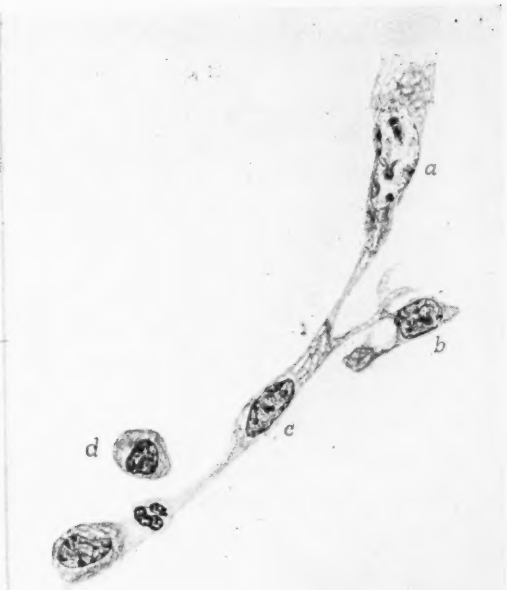

Fig. 4

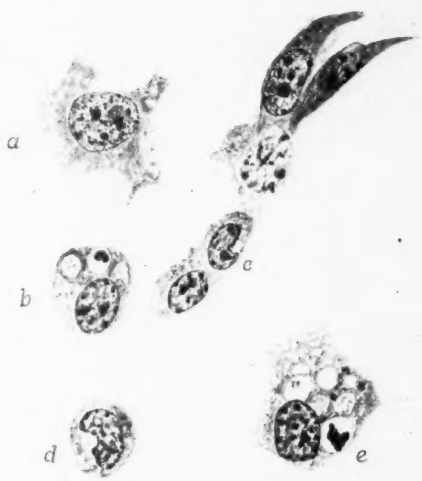

Fig. 5

blastic cells were phagocytic for polymorphonuclear leucocytes, their nuclei being crowded flatly to the side of the cell.

Comment: There was an enormous exudation of polymorphonuclear leucocytes and lymphocytes, which were rapidly transformed into small phagocytic polyblasts, scattered widely throughout the oedematous loose connective tissue.

Fibroblasts were markedly stimulated in the oedematous tissue, rounding off extensively, with early evidences of the formation of polyblasts. The proliferation of fibroblasts was very scarce. Clasmatocytes were rare.

Guinea Pig 2: Eighteen-Hour Stage: There was a somewhat less violent reaction in this animal than in the one of the preceding stage. There was less oedema, and fewer exudate cells were present in the sections studied. The accumulation of polymorphonuclear leucocytes in the clump of microörganisms was more dense, and there was more pycnosis than in the earlier stage. The small arteries in the region of the lesion were engorged with erythrocytes, but did not contain so many leucocytes as those in the previous stage. The areas of oedematous loose connective tissue contained many perivascular and scattered polymorphonuclear leucocytes, round monocytic and phagocytic polyblasts, stellate, spindle, and rounded fibroblasts, a few clasmatocytes and small, round lymphocytes. The endothelium of the blood-vessels did not show evidence of activity.

Fibroblasts showed the early response to stimulation by nuclear and nucleolar hypertrophy, basophilia of the swollen cytoplasm in which the acidophilic centrosphere became more prominent, and fragmentation or fraying of the detaching broad processes. After detachment the edges apparently became smooth and rounded. Plate 1, figures 2 and 3, shows this type of cell. There is hypertrophy of the nuclei in the cells of plate 1, figure 3, and the cell of plate 1, figure 2, contains a less irritated fibroblast nucleus.

Hypertrophied fibroblasts were occasionally seen to be transformed into clasmatocytic cells with foamy cytoplasm having pseudopodium-like processes. In the region of the lesion adjacent to muscle-sheaths, dense collections of large, monocytic cells, some of whose nuclei retain the characteristics of those of adjacent spindle cells, and others with condensed and more compact nuclear chromatin and a decrease in relative proportions of cytoplasm to nucleus, presented an appearance approaching that of lymphocytes.

Few clasmatocytes were seen, but they were more numerous here than in the earlier stage. They took the form of polyblasts; the nucleoli were not prominent and the chromatin was collected in small clumps, mainly along the pale nuclear membrane. These cells appeared to have been derived from nonhypertrophied fibroblasts, with retention of fibroblastic nuclear character.

Variations of this type of cell to those with horseshoe-shaped or lobulated nuclei were numerous. Lymphocytes were rather numerous, especially near blood-vessels. They showed evidence of changes to polyblasts.

Comment: The appearance of the attached fibroblasts was more clasmatocytic than in the preceding stage, yet their fibroblastic character was shown by their nuclear pattern. Hypertrophy of nucleus and nucleoli was more marked. Polyblast formation from fibroblasts is more extensive in this stage than in the earlier stage.

Guinea Pig Number 3: Forty-Eight-Hour Stage: The lesion occupied slightly more than one low-power field, and consisted of pink-staining, finely granular clumps of tubercle bacilli, which were penetrated and surrounded by a dense collection of exudate cells. The lesion was outlined by thin strands of pink-staining fibrils, which had the appearance of fibrin. Extending into the oedematous spaces about one low-power field on all sides, the cellular exudate was continuous with that of the lesion. In a region surrounding an included lymph node there was an inflammatory exudate which was continuous with the lesion six low-power fields away.

The accumulations of the exudate cells were not wholly associated with blood-vessels, but were rather diffuse in the oedematous loose connective tissues. The cells comprising the exudate were polymorphonuclear leucocytes and polyblasts, with round, oval, angular, or tortuous nuclei, which sometimes resembled polymorphonuclear leucocytes within the lesion. There were pycnosis and karyorrhexis of polymorphonuclear leucocytes and polyblasts. Very few lymphocytes could be identified.

In the fibrin capsule and adjacent to it were equal numbers of polyblasts and polymorphonuclear leucocytes, the polyblasts consisting of medium-sized and large forms. Many of these were phagocytic, containing polymorphonuclear leucocytes and pigment granules. The polyblasts near the bacillary clumps were angular and distorted epithelioid cells, or they had bean-shaped and horseshoe-shaped nuclei; many

were pycnotic. Here these cells outnumbered the polymorphonuclear leucocytes; lymphocytes were rare. Fibroblasts were present in the proportion of about one to fifty exudate cells. They were here rather sharply outlined against the fibrin, with their slightly basophilic foamy cytoplasm. The blood-vessels contained a moderate number of polymorphonuclear leucocytes, lymphocytes, and small polyblastic lymphocytes. The endothelium was swollen and in a number of instances cells seemed to be being constricted off into the lumen of the vessel. There was no evidence of their passing to the exterior of the vessel. There was abundant karyokinesis of these cells and of the perithelial fibroblasts, as well as moderate lymphocytic accumulation about some of the smaller vessels.

The fibroblasts were very active throughout, there being an enormous number of mitotic figures and hypertrophied, stellate cells with very large

Plate 2

FIGS. 8, 9, and 10. (Forty-eight-hour stage.) Cells from the same field, lettered significantly to show intermediate stages from fibroblasts to lymphocytic types of cells, or from fibroblasts to large, hypertrophied fibroblastic clasmatocytes, b', andpolyblasts d'; c' is a monocyte derived from a fibroblast.

FIG. 11. (Fifteen-day stage.) Large epithelioid cells, c, d, showing formation by breaking away from a chain of fibroblasts, a and b.

FIG. 12. (Fifteen-day stage.) Hypertrophied epithelioid fibroblasts of the same stage, surrounding a degenerating muscle-fibre. This suggests giant-cell formation.

nucleoli. Activity was most marked in the perithelial fibroblasts and in the muscle-sheaths. In the latter situation they formed a dense collection of cells having large oval or thick, slightly curved nuclei, with thin nuclear membranes, very little chromatin and no nucleoli, or with nucleoli less conspicuous than those of the hypertrophied fibroblasts of this stage. In many instances the cytoplasm was vacuolated or foamy, and granular with irregular, smooth, clasmatocytic margins.

Figures 8, 9 and 10 of plate 2, were all taken from the same field, one of the kind just described, within a muscle-sheath at the edge of a mass of fat cells. They represent a remarkable, closely graded series of cells, lettered significantly in series from the resting fibroblasts, a, through cells with nuclei of gradually increasing density to the darkest, round lymphocytic cell, h, the cell, d_c, representing a cell of about the stage shown in the cell, d, whose cytoplasm is vacuolated and hence the cell, d_c, resembles a clasmatocyte more than a fibroblast. The series a, b', c', d',

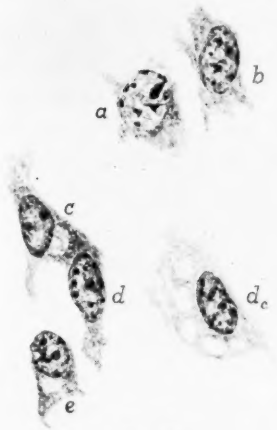

Fig. 8

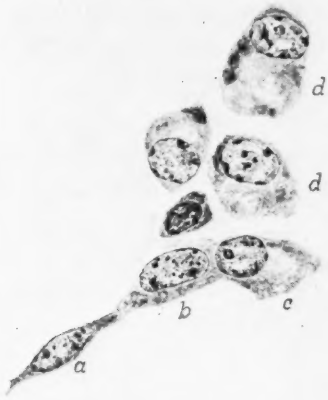

Fig. 11

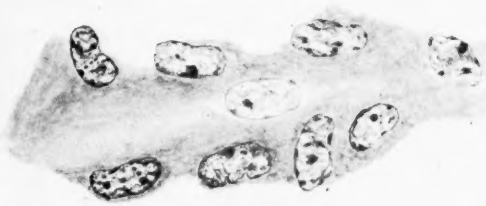

Fig. 12

Fig. 9

Fig. 10

and e' represent the other form of activity which the irritated fibroblasts take, namely, hypertrophy of the nucleus, rounding off of the cytoplasm to form large monocytic wandering cells, c', or large polyblasts, d' and e'.

Giant types of fibroblasts were numerous in the less destructive portions of the oedematous fields and in the fat cells. These areas resembled that pictured in plate 3, figure 6. Within the muscle-bundle, between the fibres, were lymphocytes and fibroblasts with dense, basophilic, diffusely granular cytoplasm and mitotic or slightly altered nucleus with hypertrophied round or irregular, red-staining nucleoli and small granules of chromatin. The monocytic cells which have been described extended into the oedematous spaces, and formed a part of the exudate. In the interfollicular connective tissue, there was much less hypertrophy of the cells, on the whole, than elsewhere, and there were more small, dark-nucleated cells resembling lymphocytes. Likewise many cells with nuclei of the resting fibroblast had rounded vacuolated cytoplasm. Figure 4, in plate 1, was taken from this area, and represents an unusual example of plasma connections between cells of widely different morphological character. It is a strong argument in support of the view that clasmatocytes and small lymphocytic cells are derivatives of fibroblasts or of the network of cells of which the fibroblast forms a conspicuous part. Fibroblasts and large mononuclear cells were actively mitotic everywhere in the stimulated tissues.

There was so much overlapping of the fibroblastic and clasmatocytic characteristics that there were few "typical" clasmatocytes. However, they could be identified in the intervals between fat cells, where they existed with polyblasts and polymorphonuclear leucocytes.

Lymphocytes were rare. In the region of the included lymph node, lymphocytes and small polyblasts occurred with large fibroblastic polyblasts, rounding fibroblasts, and occasional multinucleated giant cells. The polyblasts were distinguishable in this stage as small lymphocytic derivatives and as large, fibroblastic polyblasts. The former were more abundant near the lymph node where lymphocytes were more abundant and were absent where the lymphocytes were rare near the lesion. Horseshoe and epithelioid types were numerous, the latter being almost the only constituent of the solid exudate just inside the fibrin capsule.

Clasmatocytes also were absent near the lesion, but in certain sheaths and in solid spaces between fat cells they, with polyblasts, were numerous. Closely graded transitions between fibroblasts and clasmatocytes were also frequently seen.

The Maximow's Ziehl-Neelsen-eosin-azure stain showed that the bacilli were phagocytosed by polymorphonuclear leucocytes, polyblasts, lymphocytic clasmatocytes and epithelioid cells. There was considerable degeneration of ingested microörganisms, with beading or fragmentation of the bacilli, or deposition of yellow pigment described by Maximow. The bacilli-laden cells were numerous in the oedematous tissue surrounding the lesion, as well as in the lesion. They were rare in the distant inflammatory cells, although there was a considerable amount of pigment. Bacilli were not found within fibroblasts.

Comment: With the disappearance of lymphocytes in the lesion there was a disappearance of small polyblasts. In this stage the large fibroblastic polyblasts or small epithelioid cells were the predominant cells, with many evidences of formation from fibroblasts. Transitions between fibroblasts and clasmatocytes, fibroblasts and lymphocytes (small histiocytes?) and fibroblasts and large monocytes and polyblasts were shown. Clasmatocytes were rare. There was marked fibroblastic proliferation.

Tubercle bacilli were found in the polyblasts, epithelioid cells, polymorphonuclear leucocytes and in clasmatocytes. Yellow pigment, such as that described by Maximow as a degeneration product of tubercle bacilli, was abundant even in the areas where ingested bacilli were rare.

Guinea Pig 4: Seventy-Two-Hour Stage: The lesion, which consisted of a clump of microörganisms and masses of inflammatory cells, was almost completely surrounded by a dense capsule of fibroblasts and other closely packed cells, whose axes lay parallel to the edge of the lesion. Solid cords of this fibroblastic capsule extended into the surrounding loose tissues. From one nonencapsulated margin, the exudate extended diffusely out into the oedematous loose connective-tissue layer. The picture was much more confused than the preceding stages because of the abundance of cells. A relation of exudate to blood-vessels could not be made out.

Under the oil-immersion lens, the lesion was seen to consist of the usual polymorphonuclear leucocytes and pycnotic epithelioid mononuclear cells, between which a few spindle-shaped fibroblasts penetrated. Fibrin strands in the margin enmeshed a large number of epithelioid cells and a few polymorphonuclear leucocytes, most of which were pycnotic. Further out in the fibroblastic capsule there were more numerous unmodified lymphocytes, which were present in the same proportion as the polymorphonuclear leucocytes. Transition forms were not evident.

The fibrous capsule was composed of short, spindle-shaped embryonic fibroblasts, which tended to lie in compact parallel rows toward the inner capsular margin. It was between these rows that lymphocytes and polymorphonuclear leucocytes lay, with scattered polyblasts and epithelioid cells. An occasional clasmatocyte was recognizable. Giant cells occurred very rarely. Mitosis of fibroblasts was common.

Blood capillaries were numerous in the capsule, and contained polymorphonuclear leucocytes and lymphocytes in about equal proportions. There were occasional swelling and frequent mitoses of the blood-vessel endothelium. Unmodified lymphocytes were more numerous in the vicinity of the blood-vessels.

In the fibrin strands outside the lesion, stellate and spindle-shaped fibroblasts, clasmatocytes, polyblasts and polymorphonuclear leucocytes occurred.

Plate 3

FIG. 6. (Forty-eight-hour stage.) Mitosis and rounding-off of fibroblasts with development of some clasmatocytic characters, and intermediate stages leading to larger and smaller polyblasts as indicated by the lettering, *a* to *h*.

FIG. 7. (Forty-eight-hour stage.) Relatively quiescent fibroblasts distant from the lesion. The rounded central cell has a clasmatocytic, foamy cytoplasm.

The fibroblasts were active in this stage also, with the usual evidences of stimulation already described. Giant fibroblasts were frequently seen in the loose connective-tissue spaces and areas of fatty tissue. Near the lesion the fibroblastic polyblasts (epithelioid cells) contained a large, pale, elongated nucleus and a relatively small amount of basophilic cytoplasm.

Figure 6, plate 3, shows another transformation of fibroblasts in the muscle-sheath not far from the lesion. The striking feature of this area was the rounding up and the marked karyokinetic activity of fibroblasts. Tripolar mitosis was seen. Closely graded series of cells may be used to point out the local origin of mononuclear wandering cells. The cells were lettered in significant series, to indicate the stages leading off from the pale, relatively resting fibroblast, *a*, to cell, *h*, which showed the lobulated nucleus of a polyblast. Nearer the lesion this type of cell sometimes became much more lobulated, to resemble closely a polymorphonuclear leucocyte without granules. Some of the rounded fibro-

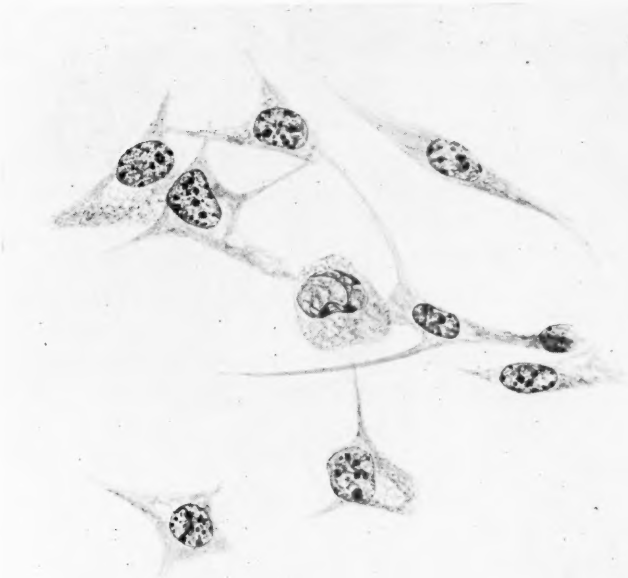

Fig. 7

Fig. 6

blasts of this area seemed to have diminished somewhat in size by frequent mitosis. Interfollicular fibroblasts were embryonic in type.

Figure 7, plate 3, represents a field found in the interfollicular tissues, where practically no evidence of stimulation was present. The central cell is a rounded fibroblast with clasmatocytic cytoplasm. The surrounding cells show varieties of nuclei and cytoplasm of very slightly irritated fibroblasts.

Comment: The significant features of the stage were the subsidence of violent, destructive changes, the extensive proliferation and abundance of embryonic fibroblasts, the extensive formation of granulation tissue about the lesion, the stimulation of the interfollicular fibroblasts, the submergence of clasmatocytic types among a preponderance of fibroblasts, and the relatively few lymphocytes associated with a diminution in number of small polyblasts.

Guinea Pig 5: Ninety-Six-Hour Stage: The lesion, consisting of densely walled-off bacillary clumps and leucocytes, with pycnotic nuclei, was the size of the diameter of one low-power field. There was a dense capsule of compact, parallel rows of embryonic fibroblasts, which formed tongue-like extensions from the surrounding cutis to the capsule. There was slight evidence of perivascular accumulation of blood cells.

Under the oil-immersion lens the centre of the lesion was occupied by pycnotic polymorphonuclear leucocytes and mononuclear cells. Spreading between these cells was a network of fine, basophilic strands. Phagocytosing epithelioid cells, with pale, distorted, elongated nuclei, were numerous inside the lesion, and the outer edge of the lesion was composed of rounded, oval, and elongated fibroblastic epithelioid cells, whose nuclear structure was very similar to that of the embryonic fibroblasts bordering the lesion, from which round cells appeared to break away to enter the lesion. There were relatively few polymorphonuclear leucocytes and occasional lymphocytes scattered through this area and between the cells of the fibroblastic capsule, where a most unusual mitosis of fibroblasts was seen.

In a few of the small blood-vessels, the endothelium was swollen, and occasionally showed evidences of a pinching-off of cells into the lumen. In most of the vessels, however, there was no evidence of endothelial activity. In the lumen of many of the vessels moderate numbers of polymorphonuclear leucocytes and occasional small and medium lymph-

ocytes were to be seen, but occasional vessels contained many small and larger monocytic cells. There was no notable evidence of a perivascular accumulation of these cells, although in the cutis there was activity of the perithelial fibroblasts.

The fibroblasts of the cutis were widely rounded off. Their basophilic, finely granular, feathery-margined cytoplasm, with its typical pale nucleus and hypertrophied nucleoli, stood out in marked contrast against the extensive, homogeneous, orange-pink background.

In the fatty layer of the subcutaneous tissue many of the fibroblasts were hypertrophied and rounded off, the cytoplasm becoming foamy, and only slightly basophilic. The centrosphere seemed to occupy almost the whole area of cytoplasm, the basophilic margin disappearing almost completely with the swelling of the cytoplasm, except for a narrow outer margin, which was seen in some cases. The fat spaces were surrounded by and occupied by many large pale polyblasts and rounded monocyte-like cells with nuclear structure resembling that of fibroblasts. There was an occasional small lymphocyte and rarely a dark, bean-shaped polyblast suggesting a lymphocytic ancestry. Intermediate stages between lymphocytes and the large epithelioid cells were rare, and evidences of fibroblastic transformation were everywhere abundant.

Clasmatocytes were not distinguishable as such, but among the embryonic fibroblasts cells of more clasmatocytic character, with dark oval nuclei and coarser chromatin clumps, occurred. Their cytoplasm was basophilic or vacuolated. These cells represent the nearest approach to clasmatocytes found at this stage.

Polyblasts were mostly of the epithelioid types, with round, slightly oval, or bean-shaped, pale nuclei and a relative increase of pale, foamy cytoplasm. There were a very few whose nuclei were dark, suggesting intermediate stages between epithelioid cells and lymphocytes.

Lymphocytes were infrequent, the majority of the cells with lymphocytic nuclei being definite small or medium-sized lymphocytes. A few lymphocytic polyblasts were seen.

Comment: Fibroblastic activity was the outstanding feature of this stage, there being few emigrated blood cells in proportion to the large numbers of epithelioid polyblasts of fibroblastic origin.

Clasmatocytes were not identifiable at this stage. Lymphocytes were relatively scarce and for the most part were untransformed, although the nuclei of some of the polyblasts were suggestive of a lymphocytic origin.

Guinea Pig 6: Nine-Day Stage: The section did not include the original lesion, but consisted of extensive infiltration of all the loose connective tissue lying between muscle-bundles, the connective-tissue sheaths of the muscles, and the subcutaneous fat.

The infiltration consisted of large numbers of polymorphonuclear leucocytes and lymphocytes of the small, medium, and large varieties, as well as clasmatocytes and macrophages, with dark, round nuclei of the clasmatocytic and lymphocytic types. There was only an occasional pale-nucleated macrophage of the fibroblastic variety. Many of the smaller vessels contained large numbers of leucocytes, of which small lymphocytes were the predominant type. The endothelium did not show evidence of activity. With the scattering of cells throughout the looser tissue, there was not a localized accumulation of exudate cells about blood-vessels. The fibroblasts here showed a widespread assumption of clasmatocytic characters. Even the pale cells with round nuclei, found in masses in muscle-sheaths of the other animals studied, were almost wholly replaced by cells with nuclei containing much more chromatin arranged in numerous fine granules. Their nucleoli were small; the cell cytoplasm was definitely more clasmatocytic than in any other stages studied.

The stimulated fibroblasts, with markedly basophilic cytoplasm and hypertrophied centrosphere, likewise in many instances possessed dark nuclei of the clasmatocytic type. In plate 1, figure 5, *a*, taken from the cutis just at the edge of the subcutaneous fat spaces, represents one of the most nearly typical resting fibroblasts to be seen in this section. The chain of cells, *c*, formed the boundary of a fat space just beneath this cell. Cell, *b*, a relatively pale, fibroblastic macrophage, was included in the fat space. The upper two basophilic cells of chain *c* are fibroblasts whose nucleoli have hypertrophied, the adjacent pale cell is a fibroblast in a relatively quiescent condition, the next cell is a polyblast, and the end cell is a monocytic cell whose nuclear structure resembles that of the macrophage, *b*. Cell *d* is a large, free polyblast found in the same field, and *e* is a dark-nucleated, phagocytic clasmatocyte found near this field.

Everywhere in the cellular areas, in all types of cells, from the round-nucleated macrophages to the giant fibroblasts so commonly seen in these tissues, the same dark, clasmatocytic nuclei were seen. Nuclei of fibroblasts lying between muscle fibres showed the same characteristics. Some attached perithelial fibroblasts were very phagocytic, and an

occasional phagocytic fibroblast showed mitosis. On the whole fibroblasts were not actively mitotic.

Although there were a few polyblasts with bean-shaped nuclei, the majority of the macrophages contained large, round, dark, diffusely granular nuclei with one or two nucleoli. There were many stages of this type of cell intermediate between large macrophages and small lymphocytes on the one hand and, on the other, relatively fewer between these macrophages and clasmatocytic fibroblasts.

There were many small, medium and large lymphocytes in this tissue. The cytoplasm of many of the mesolymphocytes was quite foamy. Phagocytosis by the lymphocytes was less common than by the oval-nucleated cells of apparent local origin, or by the large macrophages with round nuclei, between which the lymphocytes and intermediate cells were to be found. Plasma cells were fairly numerous.

Comment: The clasmatocytic character of the majority of the fibroblasts' nuclei, and evidences of the transformation of lymphocytes to epithelioid macrophages were the outstanding features in this case.

This animal showed the clasmatocytic form of activity of fibroblasts, and gave evidence of the transformation of available lymphocytes to epithelioid macrophages. The evidence for a clasmatocytic origin of the macrophages was confused by the simultaneous presence of obvious lymphocytic transformations.

Guinea Pig 7: Fifteen-Day Stage: One corner of the section was occupied by a portion of the lesion, which measured 2 by 3 low-power fields. Gross clumps of bacilli were not found, the lesion consisting of a dense exudative reaction composed of epithelioid cells, fibroblasts of various forms and degrees of irritation, and rather numerous small medium lymphocytes and scattered polymorphonuclear leucocytes. Within this general exudation were small tubercles, or collections of epithelioid cells and lymphocytes. The reaction extended out from the lesion into the loose intermuscular connective tissue for short distances, and small bundles of muscle fibres embedded in exudate cells were degenerating.

The central portion of the lesion consisted of closely packed cells whose cytoplasm for the most part could not be outlined, and whose nuclei were pycnotic. These cells included polymorphonuclear leucocytes, lymphocytes and epithelioid cells. A few small blood-vessels remained patent here. There were only occasional lymphocytes; poly-

morphonuclear leucocytes outnumbered the epithelioid cells; small Langhans giant cells were found as the edge of the lesion was approached, where there was less pycnosis, and where strands of fibroblasts and muscle-bundles were encountered. Here the polymorphonuclear leucocytes were rare, and lymphocytes that stood out rather distinctly as lymphocytes, some of which were mitotic, were fairly numerous. Plasma cells were rather frequently seen. Proceeding further from the centre of the lesion, rounded, hypertrophied embryonic fibroblasts with or without nucleoli, and with sail-like, spindle-shaped, or indefinitely rounded, foamy cytoplasm, which seemed to represent the "preëpithelioid" stage of fibroblasts, occurred. Within these areas, definite isolated epithelioid cells were to be found, some of which were obviously separating off from other more fibroblastic cells. Lymphocytes were not numerous here, and polymorphonuclear leucocytes were very rare. Rarely a solitary lymph follicle was seen.

Distant from the lesion in the loose intermuscular tissue, large fibroblastic polyblasts with round and bean-shaped nuclei occurred. These fibroblasts retained the chromatin arrangement of their nuclei, although the nucleus was markedly enlarged and the proportion between cytoplasm and nucleus had decreased.

A chain of irritated fibroblasts is pictured in plate 2, figure 11, showing the formation of an epithelioid cell by separation of one of the stimulated cells from the chain. In plate 2, figure 12, a similar chain of these stimulated fibroblasts is shown surrounding a degenerating muscle fibre. This chain of surrounding fibroblasts is not stretched, their swollen cytoplasm apparently running together to fuse with the degenerated muscle fibre.

Many gradations in size of chromatin granules and darkness of nuclear membrane, from fibroblasts to the clasmatocytic type, occurred, but there were few genuine clasmatocytes.

The blood-vessels contained only a few lymphocytes and polymorphonuclear leucocytes. About some of them were rather dense collections of lymphocytes. The general reaction was too extensive to show any definite relation to the vessels. There was no evidence of an endothelial origin of exudate cells.

Fibroblasts near the lesion lay in thin strands, or in wide bands of more or less jumbled, somewhat rounded, feathery-edged cells having large pale nuclei which contained small chromatin granules. Many

of these cells had a hypertrophied centrosphere. Adjacent to small clumps of epithelioid cells, the inner cells of the fibroblast capsule were seen to break away from the capsule as rounded epithelioid cells. Distant fibroblasts, as mentioned, rounded off to large fibroblastic polyblasts whose nuclei resembled those of resting fibroblasts. The small monocytic cell was not conspicuous in this stage, and mitosis of fibroblasts was not so frequently seen as in some of the earlier stages.

Finely graded series of stages from fibrocytes to clasmatocytes could be found in distant fields of reaction. Near lymphocytic collections an occasional evidence of clasmatocytic formation from lymphocytes was seen.

For the most part, lymphocytes stood out distinctly, without any apparent relation to the other exudate cells.

Near certain collections, however, there was evidence of a transformation of lymphocytes to polyblasts. It was impossible to trace close stages between the lymphocyte and the large, fibroblastic epithelioid cells.

Comment: A transformation of fibroblasts to epithelioid cells was the outstanding feature of this stage. Giant-cell formation by nonseparation and arrangement in a single mass of the fibroblasts, which surrounded a degenerating mass of tissue and which showed hypertrophy with epithelioid characteristics, is suggested by the evidence in this stage.

DISCUSSION

Fibroblastic activity was the most striking observation in this work. Although there are experimenters who oppose the opinion of von Möllendorff and von Möllendorff, and Knake that the "fibrocyte net" is a syncytium, in certain areas in this study there was some convincing evidence of cytoplasmic continuity between nuclei, as shown, for example, in plate 1, figure 4, and plate 2, figure 11.

There were many instances of frayed, wide bands along certain margins of stimulated cells in which the diffuse granular appearance of the cytoplasm alone marked the boundary. Just how far the nonstaining, apparently clear cytoplasm extends beyond their margins cannot be determined by this technique. I have considered, however, that the cells on the whole formed a syncytial mass, the stellate cells of plate 3, figure 7, being the form taken by cells that were in the stretched, relatively quiescent state. Reactions of these cells took various forms,

apparently depending on the length of time the toxins had acted, the toxicity of the material for the cells, the varying degrees to which the individual fibroblasts responded, and the rate of the response. For instance, the earliest effect on the fibrocyte of a mild irritant seemed to be the assumption of a clasmatocytic character, marked by condensation of the nucleus and the appearance of vacuoles in the cytoplasm (plate 1, figure 4, *c*). In this stage there was some evidence also of breaking away from the syncytium of cells with small, dark nuclei surrounded by a small amount of cytoplasm (plate 1, figure 4, *b*). These cells suggested a fibroblastic origin of some of the small, dark nucleated cells which appeared to be lymphocytes. The emigration of lymphocytes in large numbers, however, was certainly the predominant source of these small, round cells in the twelve-hour stage of this series. At the same time, in portions of the section, notably near muscle-bundles, there was an almost general rounding off of fibroblasts, some of whose nuclei seemed to represent the nonstimulated form; the majority, however, contained nuclei in which the signs of hypertrophy and assumption of embryonic characters were already present (plate 3, figure 6). Later signs were a diffusion of nuclear chromatin into a more uniform fine granulation, and hypertrophy of the red-staining nucleoli, which were easily identified (plate 2, figure 10, *b'* and *c'*). The centrosphere became more prominent than in resting cells and its acidophilic character contrasted with the finely granular basophilic rounded cytoplasm. The rounded fibroblastic cells sometimes contained resting nuclei (plate 3, figure 6) or hypertrophied nuclei (plate 2, figure 10), and sometimes resembled large lymphocytes or appeared more monocytic, with their round, polyblastic horseshoe-shaped or bean-shaped nuclei.

As fibroblastic hypertrophy increased there was a breaking away from the syncytium and a rounding-off of all stages. As a result of hypertrophy of the nuclei the type of predominant cells which separated from the syncytium varied with the degree of hypertrophy present when separation occurred. Mitosis was frequently seen in spindle-shaped cells and in cells which were rounding off.

Apparently, as a result of these two factors the divergence between the few lymphocytes and the large predominant epithelioid cells and embryonic fibroblasts of later stages was marked. There was rarely any evidence of intermediate stages between the two types. Likewise, clasmatocytes were very rare in any of the early stages. This, I believe,

may be explained by the transformation of hypertrophied fibroblasts, in which the stimulation form in this instance is not characteristic of the clasmatocyte, this type of cell, like the small histiocyte, having gradually been replaced by the larger epithelioid cells.

The almost universal assumption of clasmatocytic characters by the fibroblasts of the nine-day stage, however, with the predominance of dark-nucleated macrophages, represents clearly this one-sided clasmatocytic type of reaction. I believe that plate 2, figure 11, shows remarkably convincing evidence of the formation of epithelioid cells from hypertrophied, embryonic fibroblasts.

As further evidence of the great demand made on the fibroblasts and early-formed polyblasts, the active early phagocytosis by these forms was striking. Even the spindle-shaped cells of the early stages were very phagocytic. Rarely, as many as three polymorphonuclear cells were found crowded tightly into a single spindle-shaped fibroblast. The polyblasts of the twelve-hour stage were unusually actively phagocytic.

From this study it appears that normal connective-tissue fibroblasts represent the state of equilibrium of cells with embryonic potentialities, sensitive to stimuli in varying degrees, and responding according to the existing demand. They may be transformed into clasmatocytes, polyblasts, monocytes, epithelioid cells, plasma cells, and small histiocytes resembling lymphocytes. The scarcity of fibroblasts in the early exudate must be considered as significant. This, in view of the rarity of degenerative forms, and the presence of rounded cells with somewhat fibroblastic nuclei existing in closely graded series up to cells of a different type, I consider as significant of the using up of the typical fibroblasts in the formation, in part, of exudate cells.

It is not my purpose to discuss giant-cell formation at length, but aside from the evidence, as submitted in the literature, on the formation of the cell by fusion or by incomplete amitosis of epithelioid cells, plate 2, figure 12, strongly suggests the formation of giant cells by the nonseparation of hypertrophied, embryonic fibroblasts, which, in this instance, lying adjacent to a degenerating mass of muscle-fibre, incorporate within their syncytial mesh the degenerating protoplasmic mass. That the bordering cells of this mass are an unstretched chain of epithelioid fibroblasts similar to those seen in plate 2, figure 11, from the same slide, seems to me to be beyond doubt. It seems possible that with further degeneration and dissolution of the muscle-fibre the tendency

of the oedematous syncytium might be to arrange itself in the form typical of the Langhans giant cell.

Lymphocytes were studied in all cases, with regard to activity, emigration from blood cells, local origin, and relation to other cells. There was an extensive emigration of lymphocytes in the twelve-hour stage, when they assumed polyblastic characters within short distances from the blood-vessel. The small polyblasts predominated in the section, where they were present with polymorphonuclear leucocytes in about equal numbers.

That lymphocytes, or small histiocytes which were identical with them morphologically, were formed from fibroblasts is the obvious conclusion from the closely graded succession of stages found in a single field and illustrated in plate 2, figures 8 and 9. They are lettered in the order of progressive stages.

Because of the large amount of evidence in favor of fibroblastic activity, I have given more attention to these cells than to any other cells taking part in the formation of the exudate.

In spite of evidence of fibroblastic activity, Maximow has been unwilling to ascribe to these cells a formative rôle in exudative reactions, assuming that in inflammation the reacting cells have a haematogenous origin from lymphocytes and a histogenous origin from clasmatocytes. He recently postulated the presence in loose connective tissue of a general distribution of undifferentiated mesenchymal cells, morphologically indistinguishable from fibroblasts and entirely distinct from histiocytes or clasmatocytes. These cells occur also in lymph nodes and other haematopoietic organs and are dye-negative cells which under certain conditions can become haematopoietic. Since Maximow has not admitted any evidence of a transformation of fibroblasts to wandering cells, the theory, from a morphological point of view, is as ineffectual as if the question were left uncomplicated by the postulation of the existence of another type of cell in the loose connective tissue. The work of Cunningham, Sabin, Sugiyama and Kindwall with supravital staining, to show that the reacting cell in tuberculosis is the monocyte, introduces the same complicating factor, since these authors have also shown that this monocytic cell is one of the two types of phagocytic cells found in the connective tissues. They derived this cell from the primitive blood cell, which, like Maximow's undifferentiated mesenchyme cell, is universally distributed. Their primitive blood cell is a derivative of reticulum.

One might argue for the possible potentialities of the fibroblasts on a basis of primitiveness or relative nondifferentiation. Maximow considered the fibroblast as a highly specialized cell, without progressive potentialities, which may originate in the adult from lymphocytes, monocytes, macrophages and clasmatocytes. He found, however, that after roentgen-ray exposures the fibroblasts were the cells most affected, but he also found many polyblasts and macrophages even in the absence of lymphocytes, from which he mainly derived these cells. He could not explain the susceptibility to roentgen rays of fibroblasts, which he assumed to be highly differentiated, since the accepted theory is that roentgen rays act most strongly on the primitive, undifferentiated cells.

Maximow described certain effects of irritation of fibroblasts as the "assumption of embryonic characters," and since he could not exclude the participation of "the peculiarly embryonic" omental fibroblasts from the list of cells having progressive developmental potentialities, one is brought to consider the significance of the embryonic change. In cultures of connective tissue, Maximow found the fibroblasts much more actively mitotic than the amoeboid cells which appeared at the end of two days. Later, he saw the accumulation of fat droplets and the rounding up of stellate cells, changes which he interpreted as regressive changes leading to death.

Lang, in cultures of lung tissue inoculated with tubercle bacilli, found a tendency in some to form a mesenchymal syncytium from septal cells, instead of the more usual occurrence of isolated macrophages which also were derived from septal cells. Whether the numerous instances of mitosis seen in some of the tissues of this study and in some of the cultures of Maximow were responsible for transformations of these fibroblasts I am not prepared to say. Champy considered that during mitosis there is a tendency to loss of functional characteristics unless the normal functional demand is present. In other words, "function provokes and creates anew the differentiation after each mitosis." One excusedly asks, "What is the purpose of such abundant mitosis if the fibroblasts are purely passive cells?"

From recent work by Mallory and Parker, Foot (30), Miller (63), Rössle and Yoshida, and by Russakoff, on the relation of reticulum to collagen-formation in tubercles and elsewhere, not only has the close relation of the two types of fibrils been conclusively demonstrated, but Mallory concluded that reticulin fibrils are collagen fibrils in a looser,

less condensed form. He concluded, after finding fibroglia fibrils in reticulum cells, that reticulum cells are fibroblasts. Alfejew (2) found similarly a precollagenous formation of reticulin in embryonic membranes.

Likewise, the varied potentialities of cells, between which and fibroblasts closely graded series can be demonstrated in these tissues, strongly indicates the existence of multiple potentialities of the cell from which the interrelated forms can be traced directly or indirectly.

In my tissues (plate 2, figures 8 and 9), I demonstrated by closely related series the formation of lymphocyte-like cells from fixed-tissue cells. Kingsley found evidence of lymphocytes originating from fibroblasts. The potentialities of lymphocytes in the formation of clasmatocytes, polyblasts, macrophages, epithelioid cells and fibroblasts were described without question by Lewis and Lewis, by Maximow (58), by Awrorow and Timofejewskij, and others. Downey (22), in his work on mast cells and plasma cells found these cells originating not only from fibroblasts but also from clasmatocytes and lymphocytes. He considered that there must exist a close genetic relationship between these various cell types and the fibroblast.

I also give a demonstration of the presence in the plasma net of clasmatocytes, with evidence of breaking away from this net of a small cell whose nucleus resembles that of a lymphocyte. Von Möllendorff and von Möllendorff demonstrated the same attachment of clasmatocytes to the fibrocyte net as I have shown in plate 1, figure 4. Maximow and Lewis showed that clasmatocytes may form polyblasts and fibroblasts.

In my tissues there were very few sharply defined true clasmatocytes, but many fibroblasts contained a foamy, clasmatocytic cytoplasm with typical resting or slightly hypertrophied fibroblastic nuclei; or there were numerous closely graded forms of nuclei intermediate between the typical forms of these cells. Sabin, Doan and Cunningham distinguished monocytes from clasmatocytes by their supravital technique, yet they admitted that in malta fever and in certain other conditions the neutral-red granules in monocytes may be so numerous and large as to resemble those formed in clasmatocytes. This seems to me evidence of the dependence of the supravital staining reaction on the functional state of the cells. This reaction is not a basis for assuming the presence of two distinct types of cells. In view of the interpretation which I have made of the reactions studied, I should interpret the variations in results of Sabin and Doan between the effects of protein fractions of the tubercle

bacillus on the one hand, and the phosphatide fractions on the other, as meaning not necessarily a difference in origin of clasmatocytes and monocytes, but indicating varieties of response of the fibroblast or its derivatives (and perhaps emigrated blood cells) to the two types of toxins. This seems to me an argument for my interpretation of these results, which corresponds in part to that of von Möllendorff and von Möllendorff of the fibroblast as the primarily reacting cell in the processes studied.

Whether this reaction is specific for the tubercle bacillus, whether it is in part a foreign-body reaction, or whether it is the result of cholesterol or toxin content of this microörganism, or of other factors, it is not the purpose of this paper to determine.

I cannot state definitely that granulocytes are not formed from fibroblasts. Evidence of direct transformation was lacking, yet there was definite evidence of lobulation of polyblastic nuclei in pycnosis of the cell. According to the technique used in these tissues, one often cannot demonstrate granules in many cells that are clearly granulocytes, and again granules of ingested cells may be present in vacuoles within polyblasts after the disappearance of the nucleus of the ingested cell. Mononuclear cells with eosinophilic granules are very rarely to be found in the tissues. The nuclei of these cells resembled small lymphocytes. The early cells of myeloid metaplasia were never present; hence the usual evidence of local formation of polymorphonuclear leucocytes is entirely lacking. On the other hand, in the tissues which I studied there is abundant evidence of lobulation of pycnotic polyblasts to resemble beginning pycnosis of granular leucocytes. This is possibly the type of cell which von Möllendorff and von Möllendorff identified in their tissues as polymorphonuclear leucocytes. In their work on the mouse, in which the leucocytes are not granular, this criterion could not be used for distinction between the two types of cells, whereas in the guinea pig the granules of early developing myelocytes are quite distinct.

The "monocytes" in these tissues cannot be identified as blood monocytes, which they resemble closely, unless the origin of blood monocytes from fibroblasts be accepted as a possibility, thus changing the present conception of the origin and nature of the blood monocyte.

There is no evidence in favor of the Aschoff-Kiyono histiocytic theory of the sole participation of histiocytes in tissue reactions, but there is evidence, in the early stages, of a transformation of emigrated nongranular leucocytes, as advocated by Maximow.

CONCLUSIONS

1. The fibroblasts may be considered as an interchangeable source of cells which are involved in maintaining an equilibrium of body cells. They seem to be relatively undifferentiated cells closely related to primitive mesenchyme. The presence and degree of stimulation of these cells is evidenced by changes in type as a result of this stimulation.

2. Fibroblasts are seen to be transformed into exudate cells, including clasmatocytes, monocytes, lymphocytes (small histiocytes?), polyblasts, epithelioid cells, and, as previously shown, plasma cells and mast cells.

3. A new theory of giant-cell formation is suggested by evidence found in this study.

4. There is no evidence for the formation of polymorphonuclear leucocytes from fibroblasts; pycnotic polyblasts may become lobulated and look like pycnotic polymorphonuclear leucocytes whose granules have disappeared.

5. Monocytes may originate locally from fibroblasts, and represent intermediate stages in epithelioid-cell formation.

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OBSERVATIONS ON THE VALUE OF THE SUBCUTANEOUS TUBERCULIN TEST[1]

G. D. KETTELKAMP[2]

Tuberculin, as a diagnostic agent in tuberculosis, has been variously appraised by members of the medical profession.

There are those who contend that it is not sufficiently specific to be of value in diagnosing tuberculosis. Adams (1) claims that, several times, he has attained tuberculin hypersensitiveness in infants by the injection of colon bacilli. Zeiler and Hamel (2) have shown that in individuals injected with *B. coli*, *B. dysenteriae* and tuberculin, if later given tuberculin subcutaneously, the former tuberculin or colon-bacillus sites of injection flare up. This would show that tuberculin and colon-bacillus vaccine have something in common, but give us no idea as to how many properties tuberculin has that are not in common with the properties of colon-bacillus vaccine. According to Lash (3) the Bureau of Animal Industry makes and uses a synthetic tuberculin which seems to be even more sensitive than Koch's O.T. This makes one speculate as to what the future has in store with reference to the perfecting of a truly specific tuberculin.

There are other authors who would give the impression that tuberculin is almost one hundred per cent specific, and who would rest a diagnosis on the tuberculin reaction alone.

Some observers believe that tuberculin is very highly specific, but so sensitive that it is of little value in differentiating between active and nonactive tuberculosis. Fishberg (4) says,

> It is always found that between forty and sixty per cent of humanity react to the subcutaneous tuberculin test provided it is repeated with ascending doses three or four times. . . . . Considering that the subcutaneous tuberculin test discloses latent infection, as well as active tuberculous disease, its diagnostic value is limited, bearing in mind that over ninety per cent of humanity have been infected at some period of their lives.

The enormous amount of literature, pro and con, on these phases of the subject strongly emphasizes our lack of definite knowledge concern-

[1] Read at a meeting of the St. Louis Trudeau Club, St. Louis, Missouri, May 3, 1928.

[2] The Robert Koch Hospital, St. Louis, Missouri.

ing this potent diagnostic agent. When we once learn just what the active principle of tuberculin is, we will no doubt be more able to conclude finally regarding its action. Perhaps the work of greatest significance as bearing on this subject, which is being done to-day, is that by the committees of the various nations of the world in coöperation with the Committee of the League of Nations for the purpose of obtaining a uniform standardization of tuberculin. Few will deny that, in tuberculin as we now know it, there is something that is specific in its action on the tuberculous. Just how much these specific unknown factors are masked in their action by nonspecific factors, which still exist in tuberculin, must be answered by further investigation. Meanwhile, however, let us profit, if possible, by tuberculin as we know it.

As to the specificity of the action of tuberculin, the question is rather one of the amount or degree of specificity. While it is claimed (5) that animals infected with acid-fast bacilli other than tubercle bacilli will react to tuberculin and *vice versa* and also that focal reactions to tuberculin have been observed in nontuberculous lesions, still experimenters concede that to obtain these nonspecific reactions a much larger dose is required than that necessary for a specific reaction.

The object of this paper is to present a study of a series of patients in whom tuberculin was used for diagnosis. It deals only with patients subjected to the subcutaneous test within the past six years at the Robert Koch Hospital. All "follow-up" observations were made during the past year.

Koch's O.T. was used, and 10 mgm. was the maximum amount employed. In most cases this dose was repeated once if there had been no general reaction to the first 10 mgm. In no instance was the reaction pronounced negative unless as much as 10 mgm. had been given.

The potency of the tuberculin used was always checked in the following manner: No result was considered negative unless some other patient had reacted with fever and malaise from the use of the same stock of tuberculin.

The results of the tuberculin test have been tabulated under three headings, as follows:

1: Negative: When there was less than one degree elevation of temperature above the highest reading preceding the injection of tuberculin. Many of these negative cases showed a local skin reaction, that is, a reaction with redness and tenderness at the point of injection.

2: Nonclinical reactors: When a general reaction, consisting of an elevation of one degree or more of temperature, general aching and malaise, ensued, with no demonstrable change at a focus of infection.
3: Positive reactors: When there was an elevation of at least one degree of temperature, associated with malaise and general aching, together with evident changes at a focus of infection. These changes, in pulmonary lesions, were principally expressed by râles and, in extrapulmonary lesions, consisted of swelling or redness or pain or tenderness at the site of the lesion. When a focal reaction was suspected it was always corroborated by medical consultation before the case was charted as a positive reactor.

Except for a few cases in which individual considerations prompted a deviation from it, the following routine was employed:

The initial dose was 0.1 mgm. O.T., followed at forty-eight hour intervals by 0.5 mgm., 1.0 mgm., 5.0 mgm., 10.0 mgm., and 10.0 mgm. O.T., respectively, unless a nonclinical reaction or a positive reaction ensued before the final 10.0 mgm. dose was reached, in which case, of course, the injections were discontinued.

The following precautions were taken to further safeguard our results:

1: In the presence of acute infections, such as measles, scarlet fever, pneumonia, moribund tuberculosis, etc., the tuberculin test was not made, nor was it made on individuals who had a previous course of tuberculin therapy.
2: In case of a possible coincidental cause of the rise in temperature, such as acute colds, tonsillitis, etc., the reaction was not recorded. In some cases the tuberculin test was repeated later.
3: Two-hour observations on temperature, pulse and respiration were taken on the patients for at least forty-eight hours immediately preceding the injection of the tuberculin.
4: Two-hour observations of similar nature were taken on the patient during the tests, and each succeeding injection of tuberculin was always given forty-eight hours or more after the preceding tuberculin injection. In the great majority of the cases the interval was just forty-eight hours.
5: Only an elevation of one degree or more above the highest temperature reading preceding the tuberculin injection was considered a positive temperature reaction.
6: Patients were not allowed to exercise during the tests.
7: With but few exceptions tuberculin was not given if the patient was running a temperature as high as 99.6°, and only then if rest and other hygienic measures failed to reduce it.

As stated above, this series of cases represents the patients on whom the subcutaneous tuberculin test was made at Robert Koch Hospital since 1922, except for approximately 25 cases that received the test after these data were collected.

Since the data for this series were collected, a routine has been established at the Robert Koch Hospital of having a Schilling differential blood count recorded immediately preceding the tuberculin injections and at twenty-four to forty-eight hours after each injection, in the hope of detecting in the blood a reaction which would be more delicate than the temperature and other phases of the reaction hitherto observed. We hope to report on these results at a future date.

In our series of cases the total number of tuberculin tests was 165. The total number on whom we were able to obtain "follow-up" reports

TABLE 1

Negatives

Total		71 cases or	43	per cent of all tests made
"Follow-up" reports		31 cases or	44	per cent of all negative tests
87 per cent	Apparently well	23 cases or	74	per cent of all "follow-up" reports
	Died: cause unknown	2 cases or	6.5	per cent of all "follow-up" reports
	Died: myocarditis	1 case or	3.25	per cent of all "follow-up" reports
	Acute bronchitis	1 case or	3.25	per cent of all "follow-up" reports
Died of tuberculosis		1 case or	3.25	per cent of all "follow-up" reports
Progressive tuberculosis		3 cases or	9.75	per cent of all "follow-up" reports

was 91. Hence we have a "follow-up" report on 55 per cent of the cases tested.

The total number of negative reactions was 71, or 43 per cent of all the tuberculin tests made (table 1).

Of the negative group we were able to secure a "follow-up" report on 44 per cent. Twenty-three of these cases are apparently well, two died of causes unknown, one of myocarditis, and one was reported as suffering from acute bronchitis. If we group these as nontuberculous, in other words, if we give the negative reactions all the benefit of the doubt, it gave us the correct answer in not more than 87 per cent of the negative cases. The other 13 per cent is represented by the one case that died of tuberculosis and the three that have progressive tuberculosis. It is interesting to note here that our percentage of negative reactions among people suspected of having tuberculosis very closely approaches the minimum (4) set for all humanity.

The results on our nonclinical reactors are set forth in table 2.

The results observed here are very striking in the great number of nonclinical reactors who have fared badly. If the haemorrhage mentioned was tuberculous in origin only 59.5 per cent remained free from tuberculosis. If the haemorrhage was not due to tuberculosis and if the patient was free from active tuberculosis the percentage will still be only 62.5 per cent. It will be noticed that the morbidity in the group of nonclinical reactors is higher than it is in the positive group. For the positive group, see table 3.

TABLE 2

Nonclinical reactors

Total	56 cases or 34	per cent of all tests made
"Follow-up" reports on	32 cases or 57	per cent of nonclinical reactors
Apparently well	19 cases or 59.5	per cent of "follow-up" reports
Apparently active tuberculosis	9 cases or 28	per cent of "follow-up" reports
Died of haemorrhage (nature not mentioned)	1 case or 3	per cent of "follow-up" reports
Died of tuberculosis	3 cases or 9.5	per cent of "follow-up" reports

TABLE 3

Positives

Total positives	38 cases or 23	per cent of all tests made
"Follow-up" reports on	28 cases or 74	per cent of all positive cases tested
Negative for active tuberculosis	20 cases or 71	per cent of all "follow-up" reports
Doubtful (data insufficient)	2 cases or 7	per cent of all "follow-up" reports
Active tuberculosis	5 cases or 18	per cent of all "follow-up" reports
Died of tuberculosis	1 case or 4	per cent of all "follow-up" reports

If in the positive group we throw all the doubt toward the favoring of tuberculosis among our positive reactors, we still find that there is 71 per cent of these negative for active tuberculosis as against 87 per cent negative for active tuberculosis among our group classed as negative tuberculin reactors. We also note that the positive reactors fared better than the nonclinical reactors in the ratio of 71 to 62.5 per cent. While these percentages, at first sight, seem hard to compromise with a faith in tuberculin as a very valuable diagnostic aid in tuberculosis, a further analysis of the circumstances changes one's first impression quite materially. It has been the custom at Robert Koch Hospital, in discharging the negative cases, to advise them to observe precautions as any one

should against tuberculosis, and to report to the clinics for observation periodically, but that as far as science could determine they had not active tuberculous disease at that time. The nonclinical reactors were informed that we could not state positively whether or not they had active tuberculosis and consequently they were advised to continue a few months in sanatorium treatment because of this uncertainty. The positive tuberculin group were told that they had active tuberculosis and were advised to remain in the sanatorium at least six months longer.

Cure among incipient cases under favorable treatment is estimated as high as 75 per cent; that being true it is not surprising that 71 per cent of our positive cases should have fared well. The high percentage (74) of "follow-up" reports on these indicates that they were observing our advice, at least with respect to reporting to the clinic periodically. It would appear that the nonclinical reactors were much less on their guard, as we were able to obtain only a 57 per cent "follow-up" on them. Perhaps overconfidence was a cause of their having fared so badly.

It may be argued that the reliability of a negative tuberculin test has been set too high at 87 per cent, but I think even the most skeptical critic will allow a 75 per cent reliability. If this be so, then, if our other means of diagnosis have failed and the patient is negative to subcutaneous tuberculin, we can inform him that the chances are at least three to one that he has no tuberculosis, an assurance which is certainly worth while, and very gratifying to an anxious tuberculosis suspect. An estimation of the value of the positive reaction from our series is more difficult because of the element of recovery which enters here. But if we did make mistakes in our diagnosis of these, we at least have the great satisfaction of knowing that our error was on the side of safety for the patient. It is not at all likely that 71 per cent of these patients would have recovered their health if a large number of them had not undergone prolonged sanatorium treatment and conscientiously observed our advice on leaving the sanatorium. It is also true that these patients would not have been given this advice had they not been positive reactors.

It must be emphasized that this series of cases is small and the value of the conclusions reached is in proportion.

CONCLUSIONS

1. Unless these patients were infected subsequent to the tuberculin test a negative subcutaneous tuberculin reaction is liable to at least a 13 per cent error.

2. Nonclinical reactors should be warned of the uncertainty of their position and strongly urged to be on their guard against tuberculosis.

3. In this series the group of nonclinical reactors fared worse with the passing of years than did even the positive reactors.

4. Positive reactions are few,—only 23 per cent of all tests made.

5. Forty-three per cent of all tests made were negative.

6. The middle group, nonclinical reactors, is large, 34 per cent of the total, and a very important group from the standpoint of tuberculosis morbidity and mortality.

7. "Follow-up" reports were obtained on 55 per cent of the patients tested.

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DEXTROSE IN SYNTHETIC MEDIA FOR THE TUBERCLE BACILLUS

R. R. HENLEY[1]

For several years the laboratories of the Biochemic Division of the Bureau of Animal Industry, like most others interested in the biology of *B. tuberculosis*, have given considerable attention to synthetic media. As a basis for the work, a culture medium quite similar to those employed by Sauton (5), Frouin (1), and other French investigators was used. The composition of this medium was as follows:

Synthetic I

	grams
Asparagin	5.00
Dipotassium phosphate	1.00
Sodium citrate	0.50
Magnesium sulphate	1.00
Ferric citrate	0.06
Glycerin	70.00
	cc.
Water to make	1000.00

As may be seen, this culture fluid differs from that of Long (3) in that it contains no ammonium salts and does contain a larger percentage of glycerin. The principal idea has been to obtain a synthetic medium which would yield the greatest amount of growth per unit volume of culture medium in the shortest possible time. The basic medium, the formula for which is given above, has yielded quite regularly 0.8 to 1.0 gm. of bacteria, dry weight, per 100 cc., which is nearly double the amount obtained from a similar volume of peptonized glycerinized broth. It was, however, very interesting to note that the cultures on the beef-broth medium reached their maximum weight in three or four weeks, whereas cultures on the synthetic medium did not reach their maximum until the tenth or twelfth week. Increase in the concentration of the different constituents of the synthetic medium has resulted in better growths; for example, a yield of 1.4 gm. per 100 cc. was obtained on a medium of the following composition:

[1] Biochemie Division, Bureau of Animal Industry, U. S. Department of Agriculture, Washington, D. C.

Synthetic II

	grams
Asparagin	7.5
Dipotassium phosphate	1.5
Sodium citrate	0.75
Magnesium sulphate	1.5
Ferric citrate	0.3
Glycerin	90.0
	cc.
Water to make	1000.00

It seems probable, in view of the findings of Long and Finner (4), that the increased yield from this more concentrated medium was due in large

TABLE 1

Influence of sugars upon the growth of B. tuberculosis

MEDIUM	DRY WEIGHT BACTERIA PER 100 CC. CULTURE FLUID*	
	Four weeks	Eight weeks
	grams	grams
Synthetic II: no sugar	0.50	1.40
Synthetic II + 1 per cent dextrose	1.42	1.35
Synthetic II + 1 per cent maltose	0.76	1.37
Synthetic II + 1 per cent xylose	0.49	1.37
Synthetic II + 1 per cent arabinose	0.30	1.25
Synthetic II + 1 per cent galactose†	0.63	1.37

* Average weight of bacteria from two flasks. The maximum difference between duplicates was within 0.1 gm. except in the case of the eight weeks' cultures from the arabinose medium.

† The effect of sucrose, levulose, lactose, mannitol and dulcitol were tested in other experiments.

part to the greater proportion of glycerin, although quite recently Frouin and Guillaumie (2) have stated that the amount of growth is dependent upon the relative proportions of the different constituents, both mineral and organic, as well as upon the absolute concentration.

Since it had been noted that the addition of peptone to Synthetic I caused an increase in growth, so that at times a yield of 1.5 gm. of bacteria per 100 cc. was obtained, an attempt was made to ascertain the particular constituent of the peptone which was responsible for this marked increase in growth. A number of different amino acids were tested without result and, as the peptone contained a considerable proportion of carbohydrate, the effect on growth of various sugars was also studied. None of the sugars tested, with the exception of dextrose, had any marked effect upon the yield of bacteria. The effect of the dextrose, however, was very

striking. In four weeks 1.4 gm. of bacteria per 100 cc. were obtained from Synthetic II with dextrose added, whereas the same medium without dextrose required eight weeks for the development of an equal weight of bacteria (table 1). It appears that the principal effect of the dextrose was to increase the rate of growth. Obviously, if weighings had been made only at the fourth week it might have been concluded that the dextrose exerted a marked effect upon the total amount of growth obtainable, but by weighing at later periods it was made evident that the chief effect was upon the rate of growth during the first four weeks.

Experiments similar to the above have been repeated many times, and in every instance the media containing dextrose afforded a more rapid growth than the same media free of sugar. Dextrose was the only sugar among those tested which exerted this effect.

Different percentages of dextrose were added to the culture medium to determine the most favorable concentration. One-half of one per cent was not sufficient to produce a maximum rate, whereas 4 per cent inhibited growth, as had previously been reported by Frouin and Guillaumie (2). One per cent of dextrose appeared to be sufficient to afford a maximum rate of growth. It was interesting to observe that the reducing sugar in the culture medium steadily diminished in amount as growth increased. The precise function of the glucose has not been clear. The glycerin seemed to be used as completely in the presence of glucose as in its absence.

The formulae given above provide for a maximum of 9 per cent glycerin and 0.75 per cent asparagin. By increasing the percentage of asparagin some increase in total growth, as well as in speed of growth, was obtained and this amount was again increased by adding more glycerin. A number of trials of culture media of varying compositions were made. It seems sufficient for the purpose of this paper to state that the maximum development of the cultures was obtained upon a medium of the following composition:

Synthetic III

	grams
Asparagin	12.00
Dipotassium phosphate	1.50
Sodium citrate	0.75
Magnesium sulphate	1.50
Ferric citrate	0.30
Glycerin	100.00
Dextrose	10.00
	cc.
Water to make	1000.00

From these observations it seems clear that Frouin and Guillaumie (2) are entirely correct in their statement that not only is the actual amount of the several consitutents of the culture medium an important factor in growth, but that the yield is also influenced materially by the relative proportions of the different constitutents of the medium. The formula given above has frequently yielded in six weeks 2 gm. of bacteria, dry weight, per 100 cc. of culture fluid. Only bacteria of the human type have been used in this work.

Several precautions are necessary in order to secure the best results. Sterilization should take place in the autoclave at a steam pressure not exceeding 12 pounds for a period of no longer than twenty-five minutes. Higher pressures appear to affect the medium unfavorably. Our experience has been that 10 pounds steam pressure for twenty minutes is sufficient. The medium must be seeded from young vigorously growing cultures. Numerous tests of tuberculins prepared from these luxuriant cultures have shown, as would be expected, that they are very potent, both with respect to lethal power for guinea pigs and ability to produce skin reactions.

SUMMARY

1. Synthetic media containing dextrose afforded a more rapid growth of *B. tuberculosis* than the same media free from sugar.

2. The results confirmed the recently reported observations of Frouin and Guillaumie (2), since it was found that the growth of *B. tuberculosis* upon synthetic media was influenced by the relative proportion as well as by the actual amount of the different constituents of the media.

3. A medium is described which has afforded in six weeks yields of bacteria weighing 2 gm., dry weight, per 100 cc. of culture fluid.

The writer wishes to acknowledge his indebtedness for the valuable suggestions and advice of Dr. M. Dorset.

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EXERCISE IN PHTHISIS

I. RAPPAPORT

Exercise of the consumptive is one of the least understood problems of phthisiology; at least there is little understanding among phthisiologists on the question. Every house has its own customs; yet investigations of the physiology and pathology of exercise,—of recent years one of the most studied subjects of medicine,—have already invaded the special field of exercise in phthisis. As a matter of fact we are already in possession of some most important and scientifically exact data on the physiopathology of exercise in pulmonary tuberculosis. Knowledge is being accumulated with which phthisiologists must familiarize themselves, in order to draw practical conclusions and put them to the test of large-scale experience.

Theoretical Considerations: Hill's fundamental investigations have taught us that exercise goes with increased oxidation processes in the muscles to which respiratory and cardiac hyperfunction provide and transport the necessary oxygen. Glycogen is being broken up into lactic acid, most of which is resynthetized and one-fifth of which is burnt into carbon dioxide and water. Exercise beyond the capacity of the individual respiratory and cardiac hyperfunction is productive of an "oxygen-debt" arising from the accumulation of lactic acid in the body, that cannot be resynthetized for lack of necessary oxygen. At this point of utmost respiratory and cardiac hyperfunction falling short of supplying the necessary amount of oxygen, the phenomena of exhaustion, such as dyspnoea, cyanosis, palpitation, thoracic distress, etc., will be manifest. The oxygen-debt and fatigue that go with excessive exercise gradually wear off during the "recovery period," during which continued respiratory and cardiac hyperfunction gradually make up the oxygen-debt, and lactic acid disappears from the body. The above enumerated clinical phenomena of exercise exhaustion are also the well-known symptoms of a variety of clinical conditions. They are most conspicuously present in the genuine affections of the lungs and heart, namely emphysema and valvular disease. In the decompensating phases of these clinical con-

ditions we observe these exhaustion phenomena even when the patients are at rest. It is now a well-established fact that even under these circumstances these phenomena are due to the very same biochemical factors, namely, lactic-acid accumulation and lack of oxygen, for which circulatory or respiratory failure or (as the case may be) both are responsible. In the more or less compensated phases of these clinical conditions a combination of the symptoms is usually present to a variable degree. Anoxaemia is more or less masked by compensatory phenomena, one of which is increased oxygen consumption (as measurable by elevated basal-metabolic rate), cardiac or respiratory hyperfunction of different degrees, according to which of the organs is affected.

Experimental and Clinical Data on Exercise in Phthisis: Williamson, at the Brompton Hospital of London, investigated the interrelations of oxygen consumption, pulmonary ventilation, and respiratory quotient in pulmonary tuberculosis and found the following facts:

> For the same amount of work the consumptive not only has to begin at a higher level of ventilation but he also has to increase his ventilation by 0.75 liters per minute more than the normals. The consumptive has an increased oxygen consumption of 50 cc. per minute above that of normals. Dyspnea ensues much sooner than in normals.

Brieger, in a recent address before the medical society at Breslau, reported upon his exercise experiments carried out on consumptives with exact determinations of gas-exchanges, and computations of work-efficiency coefficients, etc. From these experiments he could show that consumptives at exercise behave precisely like cardiac patients and that the pathological phenomena are exactly the same. Pomplun carried out the *experimenta crucis* in form of a large-scale analysis of the blood gases in a great number and variety of consumptives. Pomplun showed that the arterial oxygen level of advanced cases of pulmonary tuberculosis is relatively and absolutely lowered. In the far-advanced cases an increase of the arterial carbon-dioxide content is also demonstrable.

The literature teems with records of the well-known increases of basal-metabolic rate in pulmonary tuberculosis. While it is not justifiable to enlist these records among the experimental evidences here, because we do not know just how much of the increases was due to febrile conditions, still it is safe to say that at least in a considerable number of the cases the increase was a compensatory phenomenon for chronic anoxaemia. We have been able to convince ourselves of this by determinations

of the basal-metabolic rate in a few cases of chronic nonfebrile processes, and have recorded basal-metabolic rates, in some cases 40 per cent above normal, the average being an increase of 25 per cent. From all this experimental evidence the chronic anoxaemia of advanced pulmonary tuberculosis seems to be an established fact.

All this, however, was anticipated by many phthisiologists observing the clinical phenomena in pulmonary tuberculosis. It was a well-known fact that consumptives with advanced destruction of pulmonary tissues, even in the very chronic nonfebrile form of the disease, show marked exhaustion phenomena upon exercise well within the boundaries of the normal range of safety. Other decompensation phenomena were also frequently observed, but it was not clear whether we were dealing with circulatory or respiratory decompensation. As a matter of fact the possibility of respiratory failure in pulmonary tuberculosis is not yet recognized.

In a previous paper we have called attention to the clinical phenomena observed in most consumptives when first admitted to exercise after prolonged rest, as well as to the remarkable changes seen in consumptives when on exercise. "While they are in bed they look the very picture of health belying their advanced phthisis, but no sooner are they out of bed than they turn into the typical consumptive with that peculiar hue and expression of the convalescent consumptive undergoing exercise." In the same paper we have described the clinical phenomena of chronic anoxaemia under the name of "chronic anoxaemic cardiac syndrome." It was mostly the cardiac phenomena, so preponderant in acute crises of phthisis, that impressed themselves upon our mind at the time those clinical observations were made. More recent observations and considerations, upon which we cannot enlarge here, explained in the light of the accumulating experimental evidences, have convinced us that the cardiac phenomena are only subsidiary factors of the pathological process, the main source of which is a genuine respiratory insufficiency. In advanced pulmonary tuberculosis respiratory insufficiency, progressing at the rate of pulmonary destruction, eventually leads to anoxaemia. This chronic anoxaemia is at first masked by compensatory phenomena mainly on the part of the heart, and increased oxygen consumption is an expression of the effort to make up for constant oxygen-debt. This compensation effort must be increased extensively when the consumptive goes on exercise, and pulmonary-compensation phenomena also become involved. Hence the set of clinical phenomena that will soon make their

appearance and are due to genuine respiratory decompensation. Variable degrees of exercise-exhaustion symptoms become manifest as respiratory-function efficiency has reached its limits. The order and extent of these clinical manifestations are well worth repeated discussion.

At the centre of the clinical phenomena stands the single symptom most frequently and constantly complained of in the tuberculosis ward, namely, fatigue, lassitude. From the investigations of Hill it is a fact, established beyond doubt, that fatigue is due to lactic-acid accumulation, and is the most conspicuous subjective and objective symptom of respiratory insufficiency in exercise. So it is, we believe, in pulmonary tuberculosis. That it is not only a subjective but also a very objective symptom, is evident from the experimental and clinical facts enumerated above. Fatigue and lassitude are inseparable from pulmonary tuberculosis; from its febrile incipiency to its most chronic and nonfebrile phases and forms, they always go with it. They are known to be quite independent of the activity of the pulmonary lesions. Our observations have revealed to us a parallelism between them and the extent of pulmonary destruction, as gauged by X-ray comparisons, and a reciprocal relation between them and the efficiency of compensatory hyperfunction on the part of available lung space. A remarkable fact is that cases compensated for more by cardiac hyperfunction will show fatigue symptoms even though they seem to be well compensated, as measured by available experimental and clinical tests. Here is a point deserving thorough study from both cardiological and phthisiological points of view.

The next symptom is hyperpnoea. In severe forms the rate is increased to considerably high levels and is kept there constantly. In milder cases moderate increases of rate go together with markedly increased depth of respiration, as is readily demonstrable on tracings. It should be remembered here that, while it is true that vital capacity is generally diminished in this disease, under the circumstances here discussed we have recorded considerable increases of middle capacities. Such patients have a throaty character to their voice that is frequently mistaken for hoarseness, and laryngeal involvement is looked for. In some of these cases we have been impressed by the X-ray evidences of a relatively dilated tracheal lumen, apparently an effort at dead-space reduction. Increased air-content of the available pulmonary areas, etc., phenomena of compensatory respiratory hyperfunction as manifested on the chest configuration, and fluttering of the alae nasi were also present.

The other clinical phenomena, such as increased pulse-rate at rest and palpitation on the least effort, dyspnoea, cyanosis, etc., have all been dealt with in a previous communication in connection with the chronic anoxaemic syndrome. It is to be emphasized however that dyspnoea and cyanosis are more frequent in the tuberculosis ward than is generally realized. The usual appearance of dyspnoea in the tuberculosis ward differs considerably from the commonly seen dyspnoea with forced, rapid, gasping breathing. Dyspnoea here takes the form nearer to that seen in emphysema, breathing being rather slowed and frequently even interrupted, but always very labored and accompanied by more severe distress than in any other clinical condition. Cyanosis frequently goes unrecognized in the tuberculosis ward because it does not present the same color of the patients as in other conditions. The combination of phthisical pallor and cyanosis is rather an ashen gray than the usual blue or purple color.

Practical Considerations: The practical conclusions to be drawn from all this are quite obvious. We understand now that keeping down oxygen consumption to basal levels is actually almost a causal therapy in tuberculosis of the lungs. We have now the testimony of half a century as to the superiority of rest in the treatment of pulmonary tuberculosis. If the classical prestige of this principle had to be upheld recently, against some rebellious phthisiologists, by the reassertions of G. B. Webb, these experimental and clinical data should put it back on its earlier pedestal. It is all too evident now why persistent bed-rest is so essential in the treatment of consumption even with all our active surgical methods of to-day. We know now that it is of double import, that besides holding down bodily metabolism we had to resort to local immobilization methods in order to prevent respiratory compensation efforts from involving the affected side. We know now that bed-rest has exactly the same indication in tuberculosis as in cardiac disease. We understand that dyspnoea in consumption means an increase of oxygen consumption at a rate of geometrical progression; it means that the candle is burning at both ends, and that however low the lights may be the candle must melt away. Dyspnoea and the hyperventilation going on with it have most deleterious effects on consumption. Besides breaking down the general body defense by depleting its resources in reserve, it affects also the tuberculous process in the lung locally.

Phthisiologists, who believe in autotuberculinization as a method of treatment, are correct in using exercise purposely calculated to bring

about such effects. We need not discuss the tremendous risks involved in such a procedure in face of the fact that we are utterly unable to gauge individual resources of defense and reactivity. Considering all the circumstances we must accept the fact that there is much more to be risked by putting a consumptive on exercise too early than there is by keeping him in bed longer than is needed. Before a consumptive with advanced disease is to be permitted to get out of bed a very careful investigation of his functions is in place. The generally accepted standard of longer or shorter afebrile periods as a measure of fitness is altogether inadequate. The fitness for exercise depends not only on the activity of the tuberculous process but even more so on the reëstablishment of the patient's respiratory efficiency. The extent and graduations of exercise a consumptive should be admitted to, must depend on the extent of his actual respiratory efficiency and its range of safety. To keep the patient within his range of safety we must determine his oxygen-debt, recovery period, basal oxygen consumption, the extent of compensatory phenomena he is managing to keep his balance with.

A tuberculosis patient should, of course, never be permitted to exercise to the point of dyspnoea. The point of fatigue too must be avoided unless his recovery period is not far beyond that of normal limits. The investigation as to a patient's fitness should include a careful scrutiny of the above-described clinical phenomena masking chronic anoxaemia, as they will always permit a fair approximation of the respiratory efficiency. Degrees of fatigue and general subjective feeling as measurements of fitness are too well known to need discussion, but their serious considerations should be emphasized. Exact pulse and respiratory-rate determinations, as well as recovery-period timing and the gauging of the degrees of cardiac response to effort,—holding the breath, etc.,—are most valuable bedside tests of respiratory efficiency.

Exact testing methods require the use of a Benedict apparatus. With this apparatus we can determine the oxygen consumption under basal as well as under conditions of definite and graded exercises. More important than the oxygen consumption itself is the timing of the recovery periods, which may also be made by repeated determinations of the oxygen consumption after exercise, until the preëxercise values are obtained. Of course, all these values are not absolute; they must be interpreted in the light of individual conditions. Within certain limits a patient with a great increase of oxygen consumption upon exercise is better off than another patient whose oxygen consumption is

lower but whose recovery period is too long. Oxygen-consumption levels, that do not go parallel with exercise in patients who show clinical manifestations of respiratory deficit, are most significant of respiratory decompensation. Unduly prolonged recovery periods are the measurements of respiratory insufficiency of different degrees; when correlated with the phenomena of compensatory effort,—pulse and respiratory rate, etc.,—they permit accurate determination of a patient's fitness to exercise.

Tuberculosis patients with relatively increased oxygen consumption, and increased pulse and respiratory rate, should never be admitted to exercise before we have convinced ourselves, by trial of many months, that these elevated functional levels cannot be reduced, that they have become final and are the expression of the new economy of vital functions as a result of the damage suffered. Patients with such elevated functional levels must be taught their limitations and the narrowing of the range of vital safety. They too must understand its permanent and progressive character, if they are to live rationally.

INDEX OF SUBJECTS AND AUTHORS

Abscess, lung, following tonsillectomy, Tuberculous ulceration of the bronchus in a case of, 201

Abscesses, pulmonary, Multiple, resulting from blood infection by microörganisms of the proteus group, 182

Accidental pneumoperitoneum as a complication of artificial pneumothorax, 427

Acid-fast bacilli, sources of, Some, 376

Acoustics, pulmonary, Studies on. I. An apparatus for recording respiratory sounds, 353

——, ——, —— ——. II. The transmission of tracheal sounds through freshly exenterated sheep's lungs, 360

Acute subapical versus insidious apical tuberculosis, 153

Adenitis, cervical, Tuberculous, 511

Adhesions, cauterization of, in artificial pneumothorax by the Jacobaeus-Unverricht method of closed pneumolysis, The, 233

Adult tuberculosis, A study of 1000 cases of, and its bearing on diagnosis, 99

Agglutinins, nonspecific, in tuberculosis, Observations on the occurrence of, 223

Allergic response, The testicular, (spermatocyte reaction) in guinea pigs for the diagnosis of tuberculous fluids, 55

American Indians, Tuberculosis among the, 407

Analysis of 1,000 deaths from pulmonary tuberculosis among insured policy-holders, An, 412

Apical tuberculosis, insidious, Acute subapical versus, 153

Artificial pneumothorax, Accidental pneumoperitoneum as a complication of, 427

—— ——, The cauterization of adhesions in, by the Jacobaeus-Unverricht method of closed pneumolysis, 233

Association of tuberculous lymphadenitis and genitourinary tuberculosis, The, 95

Atelectasis, pulmonary, massive, Haemoptysis in tuberculosis followed by, 310

Bacilli, acid-fast, sources of, Some, 376

Bacillus Calmette-Guérin (BCG), A study of. Biological characteristics, cultural "dissociation" and animal experimentation, 9

——, tubercle, filterability of the granular phase of the, Experiments on the, 483

——, ——, isolation of the, from sputum, The, 47

——, ——, synthetic media for the, Dextrose in, 660

(BCG), Bacillus Calmette-Guérin, A study of. Biological characteristics, cultural "dissociation" and animal experimentation, 9

——, Protective inoculation against tuberculosis with, 567

BLAIR, JOHN E., JAFFE, HENRY L., AND WIENER, J. J. The testicular allergic response (spermatocyte reaction) in guinea pigs for the diagnosis of tuberculous fluids, 55

Blood infection by microörganisms of the proteus group, Multiple pulmonary abscesses resulting from, 182

—— transfusion in pulmonary tuberculosis, 84

Blood-sedimentation index and fibrin content in tuberculous individuals, The relationship between, 559

—— test, The graphic method for the, 544

Blood-serum calcium in the negro, 350

BRANCH, ARNOLD, STEENKEN, WILLIAM, JR., AND PETROFF, S. A. A study of Bacillus Calmette-Guérin (BCG). I. Biological characteristics, cultural "dissociation" and animal experimentation, 9

Bronchiectasis, 191

Bronchus, Tuberculous ulceration of the, in a case of lung abscess following tonsillectomy, 201
BRUNN, HAROLD, AND FAULKNER, WILLIAM B., JR. Bronchiectasis, 191
BULLOCK, E. S. Remarks on tuberculous pleurisy, especially its treatments, 90

Calcium, Blood-serum, in the negro, 350
CALLAHAN, F. F., GARDINER, D. GRETH, AND GEER, EVERETT K. The use of iodized oil in pulmonary tuberculosis, 434
CALMETTE, A., AND PLOTZ, HARRY. Protective inoculation against tuberculosis with BCG, 567
Calmette-Guérin, Bacillus (BCG), A study of. Biological characteristics, cultural "dissociation" and animal experimentation, 9
Cancer of the lungs, 392
Cases of erythema nodosum with negative tuberculin tests, 447
Cauterization of adhesions in artificial pneumothorax by the Jacobaeus-Unverricht method of closed pneumolysis, The, 233
Cervical adenitis, Tuberculous, 511
Changes of the pulmonary lymph vessels in tuberculosis, Obliterative, 595
Child, negro, nine weeks old, tuberculous lesions in the lung of, A study of the. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119
Children, pulmonary tuberculosis in, A study of, 499
Clinical study of tuberculin fractions prepared from nonprotein culture media, A, 327
Clinics and state sanatoria, Philadelphia's tuberculosis patients in, The experience of, 414
Closed pneumolysis, Jacobaeus-Unverricht method of, The cauterization of adhesions in artificial pneumothorax by the, 233
Coexistent syphilis and tuberculosis, 573
Complement-fixation test in different clinical manifestations of tuberculosis, The, 212
Complication of artificial pneumothorax, Accidental pneumoperitoneum as a, 427
Compression therapy of pulmonary tuberculosis, The, 74
Connective tissue, subcutaneous, Reactions of the, to experimental tuberculosis in the guinea pig, 615
Control, tuberculosis, plan of, A unified, 580
CRIMM, PAUL D. Diaphragmatic studies in tuberculosis, 206
Crow, common, Tuberculosis of the, 134
Culture media, nonprotein, tuberculin fractions prepared from, A clinical study of, 327
CUTLER, JACOB. The graphic method for the blood-sedimentation test, 544
Cystic overflow, Recurring nontuberculous pneumonia resulting from, 174

DAVIDSON, LOUIS R. A simplified operating thoracoscope, 306
DAVIS, J. DWIGHT. Obliterative changes of the pulmonary lymph vessels in tuberculosis, 595
Deaths from pulmonary tuberculosis among insured policy-holders, An analysis of 1,000, 412
Dextrose in synthetic media for the tubercle bacillus, 660
Diagnosis, A study of 1000 cases of adult tuberculosis and its bearing on, 99
—— of tuberculous fluids, The testicular allergic response (spermatocyte reaction) in guinea pigs for the, 55
Diaphragmatic studies in tuberculosis, 206
DOLGOPOL, VERA B., AND STITT, RICHARD H. The sickle-cell phenomenon in tuberculosis patients, 454
DOUGLAS, BRUCE H., PINNER, MAX, AND WOLEPOR, BEN. Acute subapical versus insidious apical tuberculosis, 153
DUTHIE, R. C., AND MITCHELL, CHARLES A. Tuberculosis of the common crow, 134

EBERSON, FREDERICK, AND WOLFF, ERNEST. A clinical study of tuberculin fractions prepared from nonprotein culture media, 327

ELLISON, R. T., AND RAPPAPORT, I. Periodic febrile exacerbations in pulmonary tuberculosis, 440
ELRICK, LEROY. Accidental pneumoperitoneum as a complication of artificial pneumothorax, 427
Erythema nodosum with negative tuberculin tests, Cases of, 447
Exacerbations, febrile, Periodic, in pulmonary tuberculosis, 440
Exercise in phthisis, 664
Experience of Philadelphia's tuberculosis patients in clinics and state sanatoria, The, 414
Experimental tuberculosis, Reactions of the subcutaneous connective tissue to, in the guinea pig, 615
Experiments on the filterability of the granular phase of the tubercle bacillus, 483

FAULKNER, WILLIAM B., JR., AND BRUNN, HAROLD. Bronchiectasis, 191
Febrile exacerbations, Periodic, in pulmonary tuberculosis, 440
Fibrin content in tuberculous individuals, The relationship between blood-sedimentation index and, 559
Filterability of the granular phase of the tubercle bacillus, Experiments on the, 483
Fluids, tuberculous, diagnosis of, The testicular allergic response (spermatocyte reaction) in guinea pigs for the, 55
Fractions, tuberculin, prepared from nonprotein culture media, A clinical study of, 327

GALLANT, ADOLPH L. Coexistent syphilis and tuberculosis, 573
GAMBLE, W. G., JR. Blood transfusion in pulmonary tuberculosis, 84
GARDINER, D. GRETH, GEER, EVERETT K., AND CALLAHAN, F. F. The use of iodized oil in pulmonary tuberculosis, 434
GEER, EVERETT K., CALLAHAN, F. F., AND GARDINER, D. GRETH. The use of iodized oil in pulmonary tuberculosis, 434
Genitourinary tuberculosis, The association of tuberculous lymphadenitis and, 95
GOLDBERG, BENJAMIN. A unified plan of tuberculosis control, 580
Granular phase of the tubercle bacillus, filterability of the, Experiments on the, 483
Graphic method for the blood-sedimentation test, The, 544
GREISHEIMER, ESTHER M., VAN WINKLE, CHARLOTTE C., AND JOHNSON, OLGA H. The relationship between blood-sedimentation index and fibrin content in tuberculous individuals, 559
Guinea pig, Reactions of the subcutaneous connective tissue to experimental tuberculosis in the, 615
Guinea pigs, The testicular allergic response (spermatocyte reaction) in, for the diagnosis of tuberculous fluids, 55
GUNDERSEN, EDV., AND THJÖTTA, TH. The complement-fixation test in different clinical manifestations of tuberculosis, 212

Haemoptysis in tuberculosis followed by massive pulmonary atelectasis, 310
Hall, Pearl Mitchell, 1860–1928, 231
HANNON, R. R., AND LYMAN, R. S. Studies on pulmonary acoustics. II. The transmission of tracheal sounds through freshly exenterated sheep's lungs, 360
HARRELL, C. LYDON. Blood-serum calcium in the negro, 350
HARROD, CHARLES P., AND MORRIS, EVERETT. Recurring nontuberculous pneumonia resulting from cystic overflow, 174
HENLEY, R. R. Dextrose in synthetic media for the tubercle bacillus, 660
HERSOHN, WILLIAM W., AND KILDUFFE, ROBERT A. A note on the occurrence of positive Wassermann and precipitation reactions in pulmonary tuberculosis, 228
——, —— ——., —— ——, —— ——. Observations on the occurrence of nonspecific agglutinins in tuberculosis, 223
HOFFMAN, FREDERICK L. Cancer of the lungs, 392

Index, blood-sedimentation, and fibrin content in tuberculous individuals, The relationship between, 559
Indians, American, Tuberculosis among the, 407
Infection, blood, by microörganisms of the proteus group, Multiple pulmonary abscesses resulting from, 182
Inoculation, Protective, against tuberculosis with BCG, 567
Insidious apical tuberculosis, Acute subapical versus, 153
Insured policy-holders, 1,000 deaths from pulmonary tuberculosis among, An analysis of, 412
Invention, Laennec's, of the stethoscope, note on, A, 1
Iodized oil in pulmonary tuberculosis, The use of, 434
Isolation of the tubercle bacillus from sputum, The, 47

Jacobaeus-Unverricht method of closed pneumolysis, The cauterization of adhesions in artificial pneumothorax by the, 233
JAFFE, HENRY L., WIENER, J. J., AND BLAIR, JOHN E. The testicular allergic response (spermatocyte reaction) in guinea pigs for the diagnosis of tuberculous fluids, 55
JOHNSON, OLGA H., GREISHEIMER, ESTHER M., AND VAN WINKLE, CHARLOTTE C. The relationship between blood-sedimentation index and fibrin content in tuberculous individuals, 559
JOST, ELIZABETH L., AND MELLON, RALPH R. Experiments on the filterability of the granular phase of the tubercle bacillus, 483

KETTELKAMP, G. D. Observations on the value of the tuberculin test at Robert Koch Hospital, 653
KILDUFFE, ROBERT A., AND HERSOHN, WILLIAM W. A note on the occurrence of positive Wassermann and precipitation reactions in pulmonary tuberculosis, 228
KILDUFFE, ROBERT A., AND HERSOHN, WILLIAM W. Observations on the occurrence of nonspecific agglutinins in tuberculosis, 223
KING, M. J., AND MORGAN, R. H. Multiple pulmonary abscesses resulting from blood infection by microörganisms of the proteus group, 182

Laennec's invention of the stethoscope, note on, A, 1
LAGERGREN, ELSA. Cases of erythema nodosum with negative tuberculin tests, 447
LEE, L. H. An analysis of 1,000 deaths from pulmonary tuberculosis among insured policy-holders, 412
LEVINSON, A. A study of pulmonary tuberculosis in children, 499
LINDSEY, MAUDE L. Reactions of the subcutaneous connective tissue to experimental tuberculosis in the guinea pig, 615
LONGCOPE, WARFIELD T. A note on Laennec's invention of the stethoscope, 1
Lung abscess following tonsillectomy, Tuberculous ulceration of the bronchus in a case of, 201
—— of a negro child nine weeks old, tuberculous lesions in, A study of the. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119
Lungs, Cancer of the, 392
——, Miliary tuberculosis of the, with recovery, 529
LUSSMANN, F. J. The association of tuberculous lymphadenitis and genitourinary tuberculosis, 95
LYMAN, R. S., AND HANNON, R. R. Studies on pulmonary acoustics. II. The transmission of tracheal sounds through freshly exenterated sheep's lungs, 360
——, ——, ——., —— METILDI, P. F. Studies on pulmonary acoustics. I. An apparatus for recording respiratory sounds, 353
Lymph vessels, pulmonary, in tuberculosis, Obliterative changes of the, 595

Lymphadenitis, tuberculous, and genitourinary tuberculosis, The association of, 95

MAHER, STEPHEN J. Some sources of acid-fast bacilli, 376

——, —— ——. Tuberculosis among the American Indians, 407

MALKANI, MOTI. The isolation of the tubercle bacillus from sputum, 47

MARLOW, F. W., JR. Miliary tuberculosis of the lungs with recovery, 529

Massive pulmonary atelectasis, Haemoptysis in tuberculosis followed by, 310

MATSON, RALPH C. The cauterization of adhesions in artificial penumothorax by the Jacobaeus-Unverricht method of closed pneumolysis, 233

Media, culture, nonprotein, tuberculin fractions prepared from, A clinical study of, 327

——, synthetic, Dextrose in, for the tubercle bacillus, 660

MELLON, RALPH R., AND JOST, ELIZABETH L. Experiments on the filterability of the granular phase of the tubercle bacillus, 483

Method, graphic, for the blood-sedimentation test, The, 544

METILDI, P. F., AND LYMAN, R. S. Studies on pulmonary acoustics. I. An apparatus for recording respiratory sounds, 353

Microörganisms of the proteus group, blood infection by, Multiple pulmonary abscesses resulting from, 182

Miliary tuberculosis of the lungs with recovery, 529

MILLER, RICHARD H., AND SHEDDEN, WILLIAM M. Tuberculous cervical adenitis, 511

MILLER, WILLIAM SNOW. A study of the tuberculous lesions in the lung of a negro child nine weeks old. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119

Mind and tuberculosis, The, 314

MITCHELL, CHARLES A., AND DUTHIE, R. C. Tuberculosis of the common crow, 134

MOLONY, I. C. A study of 1000 cases of adult tuberculosis and its bearing on diagnosis, 99

MORGAN, R. H., AND KING, M. J. Multiple pulmonary abscesses resulting from blood infection by microörganisms of the proteus group, 182

MORRIS, EVERETT, AND HARROD, CHARLES P. Recurring nontuberculous pneumonia resulting from cystic overflow, 174

MORSE, ARTHUR H. Pregnancy and pulmonary tuberculosis, 140

Mortality, tuberculosis, in rural and urban areas, The trend of, 461

Multiple pulmonary abscesses resulting from blood infection by microörganisms of the proteus group, 182

MYERSON, M. C. Tuberculous ulceration of the bronchus in a case of lung abscess following tonsillectomy, 201

Negative tuberculin tests, erythema nodosum with, Cases of, 447

Negro, Blood-serum calcium in the, 350

—— child nine weeks old, tuberculous lesions in the lung of, A study of the. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119

Nine weeks old, negro child, tuberculous lesions in the lung of, A study of the. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119

Nonprotein culture media, tuberculin fractions prepared from, A clinical study of, 327

Nonspecific agglutinins in tuberculosis, Observations on the occurrence of, 223

Nontuberculous pneumonia, Recurring, resulting from cystic overflow, 174

Note on Laennec's invention of the stethoscope, A, 1

—— —— the occurrence of positive Wassermann and precipitation reactions in pulmonary tuberculosis, A, 228

Obliterative changes of the pulmonary lymph vessels in tuberculosis, 595

Observations on the occurrence of nonspecific agglutinins in tuberculosis, 223

—— —— —— value of the subcutaneous tuberculin test at Robert Koch Hospital, 653

Oil, iodized, in pulmonary tuberculosis, The use of, 434
Operating thoracoscope, simplified, A, 306
Overflow, cystic, Recurring nontuberculous pneumonia resulting from, 174

Patients, tuberculosis, Philadelphia's, in clinics and state sanatoria, The experience of, 414
——, ——, sickle-cell phenomenon in, The, 454
Pearl Mitchell Hall, 1860–1928, 231
Periodic febrile exacerbations in pulmonary tuberculosis, 440
PETERS, LEROY S. The compression therapy of pulmonary tuberculosis, 74
PETROFF, S. A., BRANCH, ARNOLD, AND STEENKEN, WILLIAM, JR. A study of Bacillus Calmette-Guérin (BCG). I. Biological characteristics, cultural "dissociation" and animal experimentation, 9
Philadelphia's tuberculosis patients in clinics and state sanatoria, The experience of, 414
Phthisis, Exercise in, 664
PINNER, MAX, WOLEPOR, BEN, AND DOUGLAS, BRUCE H. Acute subapical versus insidious apical tuberculosis, 153
Plan of tuberculosis control, A unified, 580
Pleurisy, tuberculous, especially its treatment, Remarks on, 90
PLOTZ, HARRY, AND CALMETTE, A. Protective inoculation against tuberculosis with BCG, 567
Pneumolysis, closed, Jacobaeus-Unverricht method of, The cauterization of adhesions in artificial pneumothorax by the, 233
Pneumonia, nontuberculous, Recurring, resulting from cystic overflow, 174
Pneumoperitoneum, Accidental, as a complication of artificial pneumothorax, 427
Pneumothorax, artificial, Accidental pneumoperitoneum as a complication of, 427
——, ——, The cauterization of adhesions in, by the Jacobaeus-Unverricht method of closed pneumolysis, 233
Policy-holders, insured, 1,000 deaths from pulmonary tuberculosis among, An analysis of, 412
Positive Wassermann and precipitation reactions in pulmonary tuberculosis, A note on the occurrence of, 228
Precipitation reactions, Wassermann and, in pulmonary tuberculosis, A note on the occurrence of positive, 228
Pregnancy and pulmonary tuberculosis, 140
Protective inoculation against tuberculosis with BCG, 567
Proteus group, blood infection by microorganisms of the, Multiple pulmonary abscesses resulting from, 182
Pulmonary abscesses, Multiple, resulting from blood infection by microörganisms of the proteus group, 182
—— acoustics, Studies on. I. An apparatus for recording respiratory sounds, 353
—— ——, —— ——. II. The transmission of tracheal sounds through freshly exenterated sheep's lungs, 360
—— atelectasis, massive, Haemoptysis in tuberculosis followed by, 310
—— lymph vessels in tuberculosis, Obliterative changes of the, 595
—— tuberculosis, Blood transfusion in, 84
—— ——, compression therapy of, The, 74
—— —— in children, A study of, 499
—— ——, iodized oil in, The use of, 434
—— ——, 1,000 deaths from, among insured policy-holders, An analysis of, 412
—— ——, Periodic febrile exacerbations in, 440
—— ——, Pregnancy and, 140
—— ——, Wassermann and precipitation reactions in, A note on the occurrence of positive, 228

RAPPAPORT, I. Exercise in phthisis, 664
——, ——., AND ELLISON, R. T. Periodic febrile exacerbations in pulmonary tuberculosis, 440
(Reaction, spermatocyte), The testicular allergic response, in guinea pigs for the diagnosis of tuberculous fluids, 55
Reactions of the subcutaneous connective tissue to experimental tuberculosis in the guinea pig, 615
——, Wassermann and precipitation, in pulmonary tuberculosis, A note on the occurrence of positive, 228

Recovery, Miliary tuberculosis of the lungs with, 529
Recurring nontuberculous pneumonia resulting from cystic overflow, 174
Relationship between blood-sedimentation index and fibrin content in tuberculous individuals, 559
Remarks on tuberculous pleurisy, especially its treatment, 90
Rural and urban areas, tuberculosis mortality in, The trend of, 461

Sanatoria, state, Philadelphia's tuberculosis patients in clinics and, The experience of, 414
Sedimentation, blood-, index and fibrin content in tuberculous individuals, The relationship between, 559
——, —— test, The graphic method for the, 544
Serum calcium, Blood-, in the negro, 350
SHEDDEN, WILLIAM M., AND MILLER, RICHARD H. Tuberculous cervical adenitis, 511
Sickle-cell phenomenon in tuberculosis patients, The, 454
Simplified operating thoracoscope, A, 306
SMITH, LUELLA H., AND WIESNER, DOROTHY E. The experience of Philadelphia's tuberculosis patients in clinics and state sanatoria, 414
Some sources of acid-fast bacilli, 376
Sources of acid-fast bacilli, Some, 376
(Spermatocyte reaction), The testicular allergic response, in guinea pigs for the diagnosis of tuberculous fluids, 55
Sputum, isolation of the tubercle bacillus from, The, 47
State sanatoria, Philadelphia's tuberculosis patients in clinics and, The experience of, 414
STEENKEN, WILLIAM, JR., PETROFF, S. A., AND BRANCH, ARNOLD. A study of Bacillus Calmette-Guérin (BCG). I. Biological characteristics, cultural "dissociation" and animal experimentation, 9
Stethoscope, Laennec's invention of the, A note on, 1
STITT, RICHARD H., AND DOLGOPOL, VERA B. The sickle-cell phenomenon in tuberculosis patients, 454
Studies, Diaphragmatic, in tuberculosis, 206
—— on pulmonary acoustics. I. An apparatus for recording respiratory sounds, 353
—— —— —— ——. II. The transmission of tracheal sounds through freshly exenterated sheep's lungs, 360
Study of Bacillus Calmette-Guérin (BCG), A. I. Biological characteristics, cultural "dissociation" and animal experimentation, 9
—— —— 1000 cases of adult tuberculosis and its bearing on diagnosis, A, 99
—— —— pulmonary tuberculosis in children, A, 499
—— —— the tuberculous lesions in the lung of a negro child nine weeks old, A. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119
Subapical, Acute, versus insidious apical tuberculosis, 153
Subcutaneous connective tissue, Reactions of the, to experimental tuberculosis in the guinea pig, 615
—— tuberculin test, value of the, Observations on the, at Robert Koch Hospital, 653
SYDENSTRICKER, EDGAR. The trend of tuberculosis mortality in rural and urban areas, 461
Synthetic media, Dextrose in, for the tubercle bacillus, 660
Syphilis and tuberculosis, Coexistent, 573

Test, blood-sedimentation, The graphic method for the, 544
——, complement-fixation, in different clinical manifestations of tuberculosis, The, 212
——, tuberculin, subcutaneous, value of the, Observations on the, at Robert Koch Hospital, 653
Testicular allergic response (spermatocyte reaction) in guinea pigs for the diagnosis of tuberculous fluids, The, 55
Tests, tuberculin, negative, erythema nodosum with, Cases of, 447
Therapy, compression, of pulmonary tuberculosis, The, 74

THJÖTTA, TH., AND GUNDERSEN, EDV. The complement-fixation test in different clinical manifestations of tuberculosis, 212
Thoracoscope, operating, simplified, A, 306
Tissue, subcutaneous connective, Reactions of the, to experimental tuberculosis in the guinea pig, 615
Tonsillectomy, lung abscess following, Tuberculous ulceration of the bronchus in a case of, 201
Transfusion, Blood, in pulmonary tuberculosis, 84
Treatment, Remarks on tuberculous pleurisy, especially its, 90
Trend of tuberculosis mortality in rural and urban areas, The, 461
Tubercle bacillus, filterability of the granular phase of the, Experiments on the, 483
—— ——, isolation of the, from sputum, The, 47
—— ——, synthetic media for the, Dextrose in, 660
Tuberculin fractions prepared from non-protein culture media, A clinical study of, 327
—— test, subcutaneous, value of the, Observations on the, at Robert Koch Hospital, 653
— tests, negative, erythema nodosum with, Cases of, 447
Tuberculosis, adult, A study of 1000 cases of, and its bearing on diagnosis, 99
—— among the American Indians, 407
——, apical, insidious, Acute subapical versus, 153
——, complement-fixation test in different clinical manifestations of tuberculosis, The, 212
—— control, plan of, A unified, 580
——, Diaphragmatic studies in, 206
——, experimental, Reactions of the subcutaneous connective tissue to, in the guinea pig, 615
——, genitourinary, The association of tuberculous lymphadenitis and, 95
——, Haemoptysis in, followed by massive pulmonary atelectasis, 310
——, Miliary, of the lungs with recovery, 529
Tuberculosis mortality in rural and urban areas, The trend of, 461
——, nonspecific agglutinins in, Observations on the occurrence of, 223
—— of the common crow, 134
—— patients, Philadelphia's, in clinics and state sanatoria, The, experience of, 414
—— ——, sickle-cell phenomenon in, The, 454
——, Protective inoculation against, with BCG, 567
——, pulmonary, Blood transfusion in, 84
——, ——, compression therapy of, The, 74
——, ——, in children, A study of, 499
——, ——, iodized oil in, The use of, 434
——, —— lymph vessels in, Obliterative changes of the, 595
——, ——, 1,000 deaths from, among insured policy-holders, An analysis of, 412
——, ——, Periodic febrile exacerbations in, 440
——, ——, Pregnancy and, 140
——, ——, Wassermann and precipitation reactions in, A note on the occurrence of positive, 228
——, syphilis and, Coexistent, 573
——, The mind and, 314
Tuberculous cervical adenitis, 511
—— fluids, diagnosis of, The testicular allergic response (spermatocyte reaction) in guinea pigs for the, 55
—— individuals, blood-sedimentation index and fibrin content in, The relationship between, 559
—— lesions in the lung of a negro child nine weeks old, A study of the. II. A tuberculous lymph node situated in the incisura interlobaris with its afferent and efferent lymphatics, 119
—— lymphadenitis and genitourinary tuberculosis, The association of, 95
—— pleurisy, especially its treatment, Remarks on, 90
—— ulceration of the bronchus in a case of lung abscess following tonsillectomy, 201

Ulceration of the bronchus, Tuberculous, in a case of lung abscess following tonsillectomy, 201
Unified plan of tuberculosis control, A, 580

Urban areas, rural and, tuberculosis mortality in, The trend of, 461
Use of iodized oil in pulmonary tuberculosis, The, 434

Value of the subcutaneous tuberculin test, Observations on the, at Robert Koch Hospital, 653
VAN WINKLE, CHARLOTTE C., JOHNSON, OLGA H., AND GREISHEIMER, ESTHER M. The relationship between blood-sedimentation index and fibrin content in tuberculous individuals, 559
Vessels, lymph, pulmonary, in tuberculosis, Obliterative changes of the, 595

Wassermann and precipitation reactions in pulmonary tuberculosis, A note on the occurrence of positive, 228
WIENER, J. J., BLAIR, JOHN E., AND JAFFE, HENRY L. The testicular allergic response (spermatocyte reaction) in guinea pigs for the diagnosis of tuberculous fluids, 55
WIESNER, DOROTHY E., AND SMITH, LUELLA H. The experience of Philadelphia's tuberculosis patients in clinics and state sanatoria, 414
WILSON, JULIUS L. Haemoptysis in tuberculosis followed by massive pulmonary atelectasis, 310
WOLEPOR, BEN. The mind and tuberculosis, 314
——, ——, DOUGLAS, BRUCE H., AND PINNER, MAX. Acute subapical versus insidious apical tuberculosis, 153
WOLFF, ERNEST, AND EBERSON, FREDERICK. A clinical study of tuberculin fractions prepared from nonprotein culture media, 327